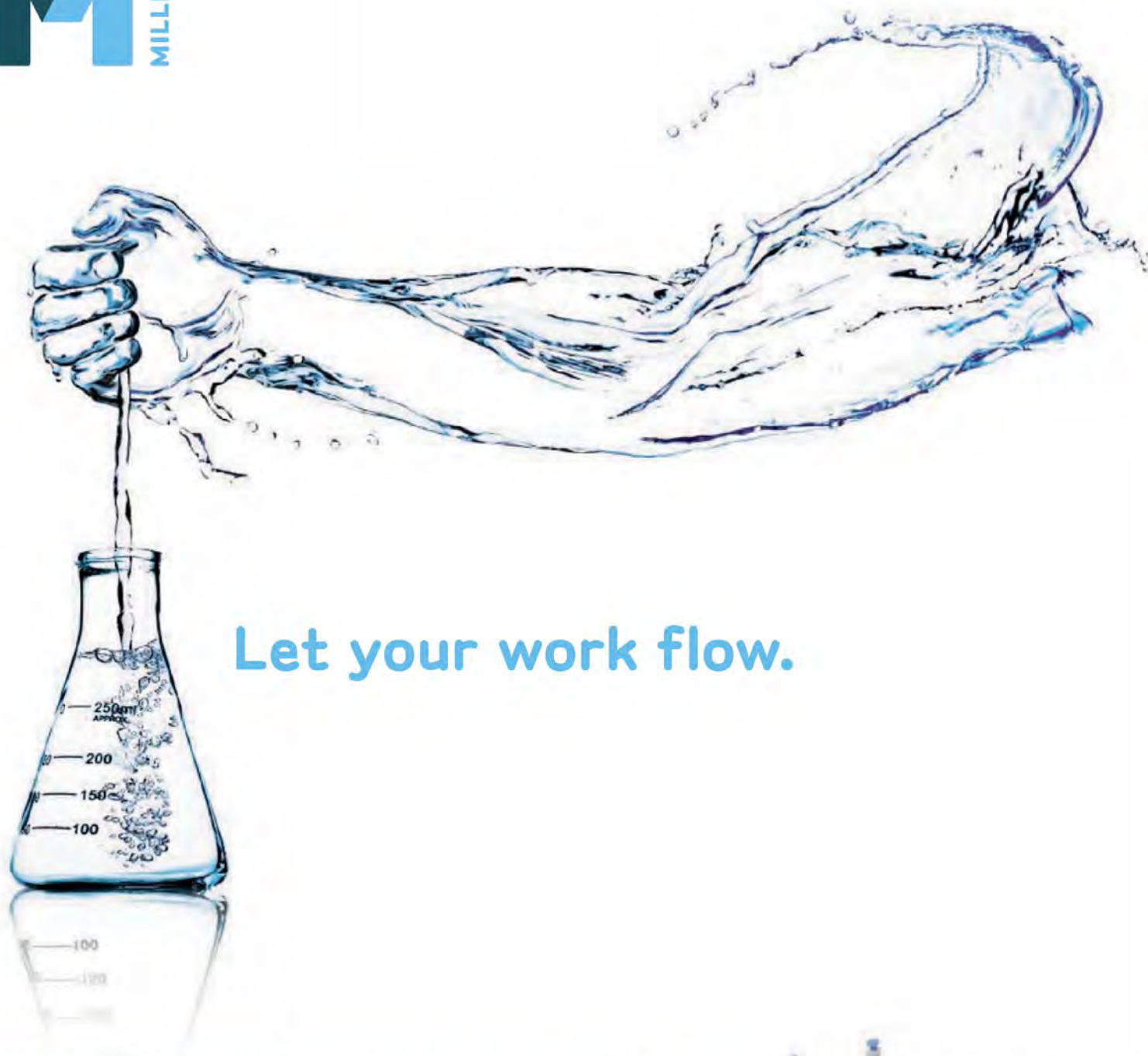


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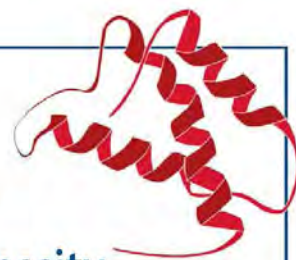
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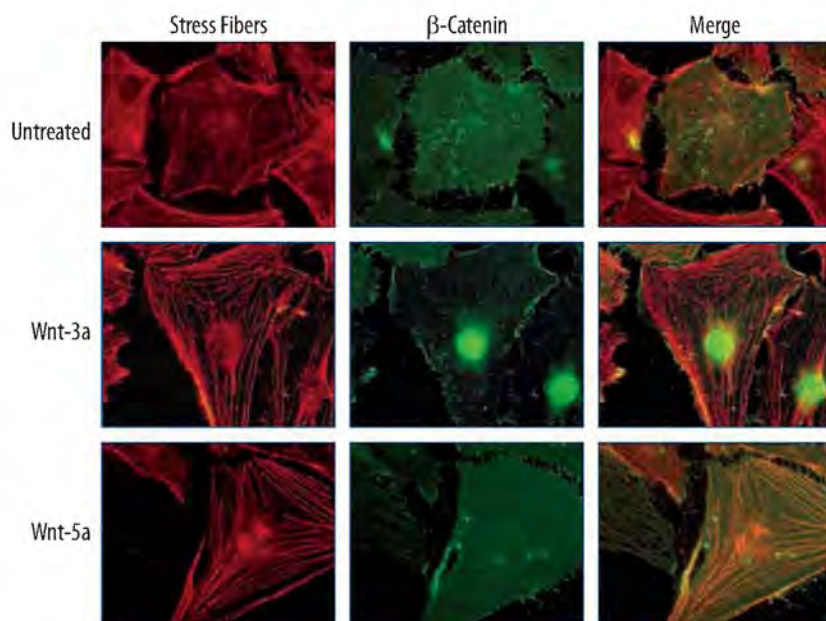
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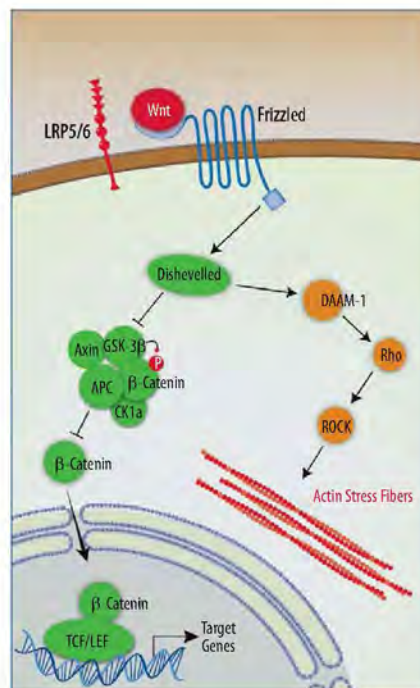
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Photo: Haraldr Stefansson/Alamy

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1700 Antennal Circadian Clocks Coordinate Sun Compass Orientation in Migratory Monarch Butterflies

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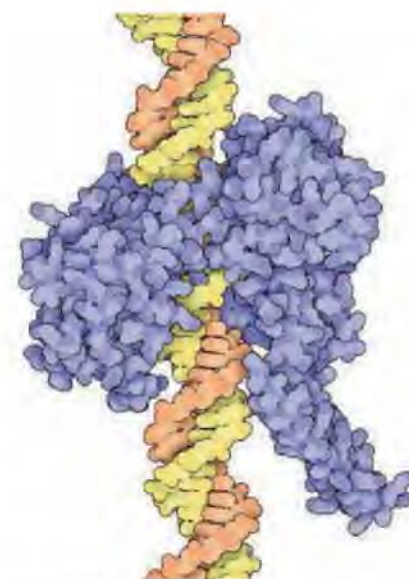
Monarch butterfly antennae contain the timing mechanism for time-compensated Sun compass orientation.

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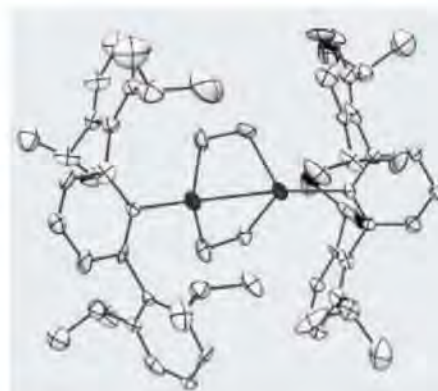
1705 Optimizing Influenza Vaccine Distribution

J. Medlock and A. P. Galvani

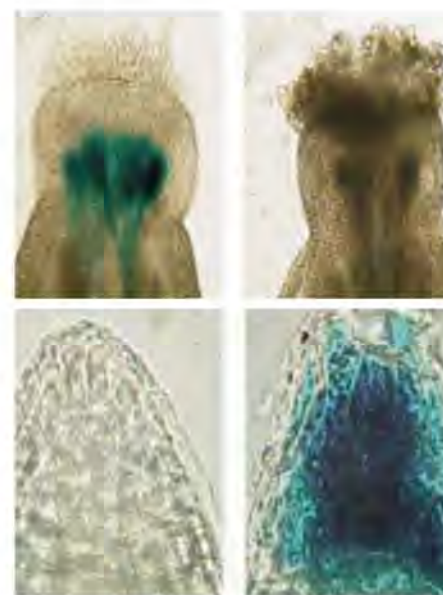
Age-related transmission patterns should be incorporated into vaccine distribution policy to minimize the impact of epidemics.



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J.-E. Kang et al.

Sleep patterns can influence amyloid plaque formation in a mouse model of Alzheimer's disease.

10.1126/science.1180962

Detection of Gamma Rays from a Starburst Galaxy

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Temporal and Spatial Variability of Lunar Hydration as Observed by the Deep Impact Spacecraft

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10.1126/science.1179788

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10.1126/science.1181471

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Comment on "Infants' Perseverative Search Errors Are Induced by Pragmatic Misinterpretation"

J. P. Spencer et al.

full text at www.sciencemag.org/cgi/content/full/325/5948/1624-a

Response to Comment on "Infants' Perseverative Search Errors Are Induced by Pragmatic Misinterpretation"

J. Topál et al.

full text at www.sciencemag.org/cgi/content/full/325/5948/1624-b

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Finding may point to future treatments for human colorblindness.

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RESEARCH ARTICLE: The Single Transmembrane Domains of Human Receptor Tyrosine Kinases Encode Self-Interactions

C. Finger et al.

The transmembrane domain of any of the 58 human receptor tyrosine kinases is sufficient to mediate dimerization.

RESEARCH ARTICLE: MSK2 Inhibits p53 Activity in the Absence of Stress

S. Llanos et al.

The kinase MSK2 inhibits p53 transcriptional activity at a subset of promoters through a kinase-independent mechanism.

PERSPECTIVE: Integrin Proteomes Reveal a New Guide for Cell Motility

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A proteomics analysis of integrin-associated complexes establishes an unexpected connection to cell migration.

PERSPECTIVE: Human-Specific Genes May Offer a Unique Window into Human Cell Signaling

P. D. Stahl and M. J. Wainszelbaum

Analysis of human-specific genes may reveal, at the molecular level, what makes humans human.

GLOSSARY

Find out what APR, NHEJ, and SLAM mean in the world of cell signaling.

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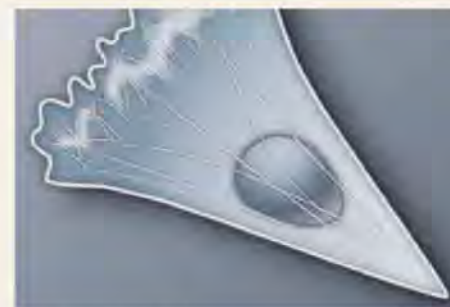
S. McLoone

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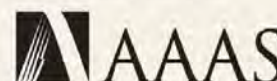
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Butterfly Navigation >>

Monarch butterflies migrate to Mexico from various parts of North America in the fall and navigate with the aid of Sun compass. This navigational mechanism, also employed by migratory birds, uses the circadian clock to compensate for the positional change of the Sun in the sky throughout the day. The mechanism behind time-compensated Sun compass orientation has remained obscure. **Merlin *et al.*** (p. 1700; see the Perspective by **Kyriacou**) now provide comprehensive data showing that the mechanism resides in the antennae of the butterflies, rather than the brain, as previously thought. The "antennal clocks" found in the monarchs probably provide the primary timing mechanism for Sun compass orientation. These findings reveal a further function for the antennae—a function that may extend widely to other insects that use this orientation mechanism.



Facile Fluorination

Fluorine atoms have become a useful substituent in pharmaceuticals. However, they remain challenging to introduce synthetically because present methods for carbon-fluorine bond formation require either corrosive conditions or somewhat exotic, and thus expensive, reagents. A sticking point has been the failure of traditional palladium catalysts to couple aryl groups with coordinated fluoride. **Watson *et al.*** (p. 1661, published online 13 August; see the Perspective by **Gouverneur**) show that pairing palladium with a well-designed phosphine ligand produces a versatile catalyst for aryl fluorination using simple fluoride salts. The method tolerates a range of functional groups and should facilitate efficient syntheses of multiple fluoroaromatic targets.

Martian Impact

Impact craters form frequently on Mars, exposing material that would otherwise remain hidden below the surface. **Byrne *et al.*** (p. 1674) identified mid-latitude craters that formed over the last few years, imaged them in great detail with a camera on board the Mars Reconnaissance Orbiter, and monitored subsequent changes. The craters excavated buried water ice, which was later seen sublimating away. In addition, some craters might have excavated completely through the ice. The observations are consistent with models and other observations that suggest water ice should be stable decimeters to about 1 meter below the martian



surface at latitudes poleward of about 40°; and suggest that, in the recent past, Mars had a wetter atmosphere than at present.

Polymer Photodetectors

Optical sensing is used in a wide range of applications, such as low-light detection systems in cars and cameras. Most photodetectors have a limited spectral range and can only detect a narrow range of wavelengths. **Gong *et al.*** (p. 1665, published online 13 August) developed polymer photodetectors with extremely broad spectral response and exceptionally high sensitivity that can exceed the response of an inorganic semiconductor detector at liquid helium temperature. A key aspect in the device design is the inclusion of blocking layers to reduce significantly the dark current or noise in the devices.

Tin Two-Step

Doubly and triply bonded carbon compounds have a well-studied tendency to link up with one another and form rings. The rates of these reactions and their relative susceptibilities to acceleration by heat versus light are encapsulated in the decades-old Woodward-Hoffmann rules. More recently, alkene and alkyne analogs have been prepared with heavier elements such as silicon and tin substituted for carbon. **Peng *et al.*** (p. 1668; see the Perspective by **Sita**) have now discovered that two distannynes (compounds with triply bonded tins) react readily with ethylene to form cycloadducts, with tin-carbon σ bonds taking the place of C-C and Sn-Sn π bonds. These

products, characterized spectroscopically and crystallographically, are only loosely bound at room temperature, easily reverting to their multiply bonded precursors on gentle heating.

Together

Two of the most important questions in paleoclimatology are, how are the climates of the Northern and Southern Hemispheres linked, and what are the roles of the high latitudes and the tropics in driving and transmitting climate changes? Past investigations have concentrated on the study of large, rapid climate changes like deglaciations or the Younger Dryas because they are the easiest ones to see and to date. **Licciardi *et al.*** (p. 1677) expand the scope of these investigations by determining precise cosmogenic isotope ages for glacial moraines formed in the Peruvian Andes during the Holocene (the last 11,000 years). The precision of these data reveals a broad correlation between Peruvian glacial advances and climate in the North Atlantic region, revealing important climate linkages between the tropics and higher latitudes.

Malaria Chloroquine Resistance Transporter

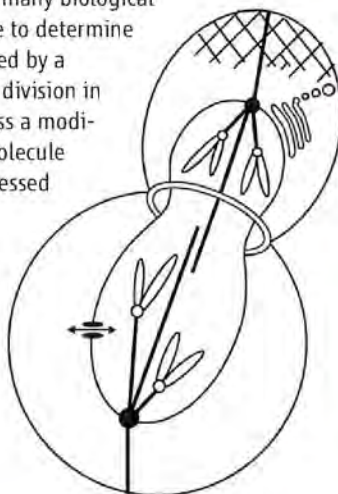
Malaria is one of the most deadly infectious diseases in the world today, and the emergence and spread of chloroquine-resistant parasites has been a disaster for world health. The Chloroquine Resistance Transporter (PfCRT) was originally identified because mutations in this protein confer chloroquine resistance in the human malaria parasite, *Plasmodium falciparum*. However, the mechanism by which they do so has

CREDITS (TOP TO BOTTOM): MONARCH WATCH; BYRNE ET AL.

been the subject of ongoing debate. **Martin *et al.*** (p. 1680) have now succeeded in expressing PfCRT at the surface of *Xenopus laevis* oocytes, establishing a robust and reproducible heterologous system for the study of this protein. The resistance-conferring form of the protein mediates the transport of chloroquine, whereas wild-type PfCRT does not. Thus, as suspected, chloroquine resistance in the malaria parasite indeed arises as a result of the transport of the drug via mutant PfCRT.

Cataloging Kinase Targets

Protein phosphorylation is a central mechanism in the control of many biological processes (see the Perspective by **Collins**). It remains a challenge to determine the complete range of substrates and phosphorylation sites altered by a kinase like cyclin-dependent kinase 1 (Cdk1), which controls cell division in yeast. **Holt *et al.*** (p. 1682) engineered a strain of yeast to express a modified Cdk1 molecule that could be inhibited by a specific small-molecule inhibitor. The range of Cdk1-dependent phosphorylation was assessed by quantitative mass spectrometry, which revealed many previously uncharacterized substrates for Cdk1. In addition to phosphorylation on serine and threonine residues, which appears to be evolutionarily ancient, tyrosine phosphorylation occurs primarily in multicellular organisms. **Tan *et al.*** (p. 1686, published online 9 July) compared the overall presence of tyrosine residues in human proteins (which are frequently phosphorylated) and in yeast proteins (which are not). Loss of tyrosine residues has occurred during evolution, presumably to reduce adventitious tyrosine phosphorylation.



From Retrogene to Phenolic Metabolism

Metabolic plasticity, which involves the creation of new genes, is an essential feature of plant adaptation and speciation. Studying plants from the mustard family, **Matsuno *et al.*** (p. 1688) show that variants of the cytochrome P450 enzyme family were derived through retroposition, duplication, and subsequent mutation. Evolutionary changes increased the volume of the substrate pocket altering with what sorts of substrates the enzymes could interact. The enzymes formed the basis for a new metabolic pathway, the products of which include constituents of pollen and of phenylpropanoid metabolism.

Character Transplant

When engineering bacteria, it can be advantageous to propagate the genomes in yeast. However, to be truly useful, one must be able to transplant the bacterial chromosome from yeast back into a recipient bacterial cell. But because yeast does not contain restriction-modification systems, such transplantation poses problems not encountered in transplantation from one bacterial cell to another. Bacterial genomes isolated after growth in yeast are likely to be susceptible to the restriction-modification system(s) of the recipient cell, as well as their own. **Lartigue *et al.*** (p. 1693, published online 20 August) describe multiple steps, including *in vitro* DNA methylation, developed to overcome such barriers. A *Mycoplasma mycoides* large-colony genome was propagated in yeast as a centromeric plasmid, engineered via yeast genetic systems, and, after specific methylation, transplanted into *M. capricolum* to produce a bacterial cell with the genotype and phenotype of the altered *M. mycoides* large-colony genome.

Rethinking Vaccine Distribution

The distribution of vaccines is a complex issue lying at the intersection of public health, economics, and ethics and it cannot be decided in hindsight as an epidemic unfolds. Thus, mathematical modeling can be valuable for guiding policy, and **Medlock and Galvani** (p. 1705, published online 20 August) present an analysis of how to distribute influenza vaccine among different age groups in a way that will minimize transmission. Scenarios were developed for different outcomes that tell us what happens, in terms of numbers of infections, mortality, and cost, when various cohorts are targeted for vaccination under different epidemic conditions, and compare 1918- and 1957-like epidemics. The scenarios could apply equally well to antiviral drug distribution. The conclusion is that the current recommendations for vaccine distribution from the U.S. Centers for Disease Control and Prevention may need to be revised to include age-related patterns of transmission to minimize the impact of epidemic influenza.

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Science Careers

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Steven Chu is the U.S. Secretary of Energy and a Nobel Laureate in physics.

Carbon Capture and Sequestration

OVERWHELMING SCIENTIFIC EVIDENCE SHOWS THAT CO₂ EMISSIONS FROM FOSSIL FUELS HAVE caused the climate to change, and a dramatic reduction of these emissions is essential to reduce the risk of future devastating effects. On the other hand, access to energy is the basis of much of the current and future prosperity of the world. Eighty percent of this energy is derived from fossil fuel. The world has abundant fossil fuel reserves, particularly coal. The United States possesses one-quarter of the known coal supply, and the United States, Russia, China, and India account for two-thirds of the reserves. Coal accounts for roughly 25% of the world energy supply and 40% of the carbon emissions.* It is highly unlikely that any of these countries will turn their back on coal any time soon, and for this reason, the capture and storage of CO₂ emissions from fossil fuel power plants must be aggressively pursued.

This special issue of *Science* discusses the potential role of carbon capture and sequestration (CCS) in reducing CO₂ emissions. The scale of CCS needed to make a significant dent in worldwide carbon emissions is staggering. Roughly 6 billion metric tons of coal are used each year, producing 18 billion tons of CO₂. In contrast, we now sequester a few million metric tons of CO₂ per year. At geological storage densities of CO₂ (~0.6 kg/m³), underground sequestration will require a storage volume of 30,000 km³/year. This may be sufficient storage capacity, but more testing is required to demonstrate such capacity and integrity.

We should pursue a range of options for new coal-fired power plants (such as coal gasification, burning coal in an oxygen atmosphere, or postcombustion capture) to determine the most cost-effective approach to burn fuel and reduce the total amount of CO₂ emitted. No matter which technology ultimately proves best for new plants, we will still need to retrofit existing plants and new plants that will be built before CCS is routinely deployed. Each new 1-gigawatt coal plant is a billion-dollar investment and, once built, will be used for decades.

Estimates of CCS costs vary considerably, but experience with other pollution control technologies such as the scrubbing of SO₂ and NO_x show that costs can be considerably lower than initial estimates. Furthermore, new ideas are now being explored, such as more efficient, lower-temperature catalytic conversion of coal to hydrogen and methane, CO₂ capture based on phase separation, and polygeneration (production of variable mixtures of electricity, methane, liquid fuel, and ammonia). In the natural world, sequestration of CO₂ occurs through photosynthesis, calcification of CO₂ by phytoplankton, and mineralization in ground root systems. Can we enhance natural processes ("reforestation plus") or draw inspiration from nature as a starting point for artificial capture? Similarly, nature provides proof that the energy penalty for releasing adsorbed CO₂ in postcombustion capture can be decreased: Through carbonic anhydrases, our blood captures CO₂ created by cell metabolism and releases it in the lungs with no enthalpic energy penalty.

Public support of CCS R&D is essential, and for this reason, \$3.4 billion of American Recovery and Reinvestment Act money is being invested by the U.S. Department of Energy (DOE) in CCS R&D. The DOE is also supporting the testing of CO₂ sequestration in seven different U.S. geologic formations. To accelerate global dissemination of CCS technology and expertise, international collaborations are essential. The G-8 leaders called for at least 20 CCS projects by 2010. In July, I announced a new U.S.-China Clean Energy Research Center that will facilitate joint research in several areas, including CCS. Intellectual property developed jointly will be shared between our countries.

There are many hurdles to making CCS a reality, but none appear insurmountable. The DOE goal is to support R&D, as well as pilot CCS projects so that widespread deployment of CCS can begin in 8 to 10 years. This is an aggressive goal, but the climate problem compels us to act with fierce urgency.

— Steven Chu

10.1126/science.1181637



*<http://energy.gov/carbongraph>

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EDUCATION

Seeds of Knowledge

Teaching science as a set of accumulated facts can fail to convey the process whereby scientists discovered those facts. As science education experts urge teachers to shift toward a more process-centered pedagogy, the question arises of how early in the schooling process such an approach can be implemented. Smith *et al.* present the results of a series of lessons in which kindergarten students (5 to 6 years old) actively participated in uncovering the properties of seeds. Instead of simply learning key words relating to seed growth, students took part in a directed discussion modeled after a scientific conference, in which they could share ideas and learn from each other. After raising conflicting ideas over what defines a seed, the students were guided to design experiments in order to test their ideas and reach a resolution. Seeds (and non-seeds) were planted under a variety of different conditions, and students recorded their daily observations, methods, and ideas for future experiments in their science notebooks. A second conference was then held to discuss the results. The conference discussions suggested even quite young children are capable of engaging in scientific reasoning. — MM

Sci. Children **47**, 48 (2009).

BIOMEDICINE

Friend and Foe Alike

The immune system protects against infection and disease, but there are numerous examples where it has switched sides, as in autoimmune diseases and in cancer. Cells become cancerous when they acquire genetic mutations that enable them to evade the regular controls on growth. In addition, stomach (*Helicobacter pylori*) and liver (hepatitis viruses B and C) cancers have been associated with infection-induced inflammation, which involves immune cells, such as macrophages, and inflammation signaling molecules that can promote tumorigenesis. Research on the mechanisms of inflammation-induced carcinogenesis has focused mainly on the innate branch of the immune system, primarily the NF- κ B intracellular signaling pathway.

Colorectal cancer has been linked to inflammation of the colon (colitis), which can be caused by bacterial infections. Wu *et al.* have found that the human bacterium enterotoxigenic *Bacteroides fragilis* (ETBF), which induces colitis, can promote colon cancer in a mouse model of the disease. They

observed that ETBF activated the transcription factor Stat3 and promoted the generation of interleukin-17 (IL-17)—producing T helper cells (T_H-17 cells). Blocking IL-17 with neutralizing antibodies inhibited ETBF-induced colon cancer in these mice. Thus, colorectal cancer in humans may be caused by bacterial infection and mediated by a T cell immune response. — HP

Nat. Med. **15**, 1016 (2009).

MATERIALS SCIENCE

Squeezing Holes

Most materials stretched in one dimension will contract in the other two, a property captured in the substrate's positive Poisson's ratio. Auxetic materials, in contrast, expand in a lateral direction when stretched, or correspondingly



PLANT SCIENCE

Support Shoots, Repress Roots

Most flowering plants grow at both ends. The growth of leaves and flowers derives from the shoot apical meristem, and the growth of roots derives from the root meristem. Although the meristems, which are clusters of undifferentiated stem cells, have much in common, they generate different tissues and structures. Studying the small mustard plant *Arabidopsis*, Grigg *et al.* offer an analysis of how the meristems come to differ. Two homeodomain proteins, PHABULOSA (PHB) and PHAVOLUTA (PHV), support shoot apical meristem development and repress root meristem development. PHB and PHV are regionally repressed by a microRNA pathway, and this enables development of the root meristem. This regulatory network is in place as early as the 32-cell stage of embryonic development, when the root stem cells begin to emerge. Repression of PHB and PHV seems to be particularly important for establishing the quiescent center cells of the root meristem. — PJH

Curr. Biol. **19**, 1485 (2009).

shrink in a lateral direction when compressed. Bertoldi *et al.* consider a two-dimensional rubber sheet punctuated with an array of circular holes that shows auxetic behavior only under compression. The sheet initially has a positive Poisson's ratio, which decreases with increasing compressive strain. The holes deform into orthogonal ellipses, as there is insufficient space for all of them to collapse in the same direction. Using finite element simulations, the authors find that a minimum void fraction of 0.34 is needed in order to obtain auxetic behavior. Below this value, the compression leads to a macroscopic instability whereby an entire row of holes collapses to accommodate the strain, leaving the rest of the sample mostly undeformed. The void density also influences the critical strain at which the Poisson's ratio becomes negative; thus, it should be possible through engineering the specific void pattern to make a highly tunable compressively auxetic material. — MSL

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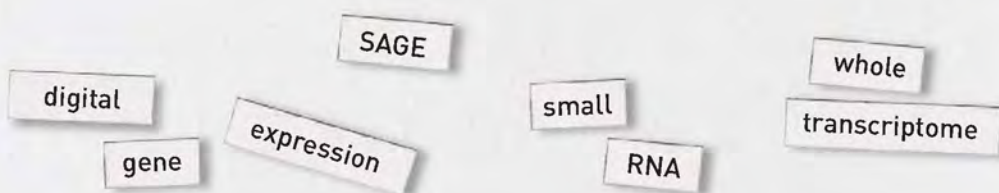


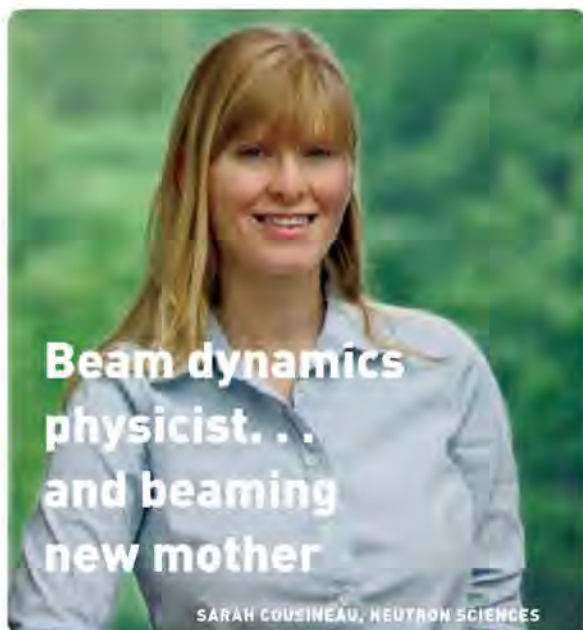
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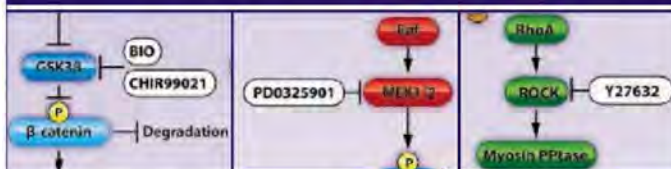
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Dealing With Denial

Paul Ehrlich is still out to save the world. A generation after sounding the alarm about overpopulation, the Stanford University biologist and colleagues have launched an effort called MAHB (pronounced "mob")—the Millennium Assessment of Human Behavior. Its aim is to penetrate public apathy and denial and prod social scientists to look into the behavioral aspects of Earth's problems.

"I'm trying to ... get a global discussion going," says Ehrlich. Science has laid out the problems—climate change, food and water crises, loss of biodiversity, and toxins in the environment—in great detail, the group argues on a new Web site, mahb.stanford.edu, "yet society stubbornly refuses to take comprehensive steps to deal with them and their drivers," the first of which is population growth. When Norman Borlaug, father of the Green Revolution, died last week, "the blogs were full of 'This is the person who proved Ehrlich wrong'" in his dire prophecies, says Ehrlich. "What we need is a total change in the way we think about these problems. ... We need to start talking very frankly about what people want and what they can have."

Ehrlich, 77, says that at present MAHB's core group, including atmospheric scientist Stephen Schneider and Donald Kennedy, former editor-in-chief of *Science*, is focusing on getting the word out. A "world megaconference" is planned for 2011.



on plutonium who has assisted with past U.S. efforts to communicate with North Korea's nuclear scientists. Goodenough, 87, developed the component of lithium-ion batteries known as the cathode, a ubiquitous part of consumer electronics and hybrid cars.

Boys Will Be Boys

A 2006 survey of online video gamers revealed that 85% were male. Why the skew? Evolution, say researchers at the University of Missouri, Columbia.

Psychology graduate student Jonathan Oxford and colleagues recruited 42 undergraduate men, divided them into teams of three, and measured the testosterone levels in their saliva before and after they played a violent video game, *Unreal Tournament 2004*. Each participant played two game types: Death Match, in which teammates battled one another, and Onslaught, in which teammates cooperated to fight another team. The researchers found that competition raised testosterone levels more when men battled "outgroups" than when they vied with a fellow team member.



The results bear out the notion, which has also been suggested in sports studies, that fighting as a team taps into males' evolved propensity for engaging in "coalitional male-male competition," the authors report in an article in press in *Evolution and Human Behavior*. "Beating a teammate ... does not result in a testosterone surge and may even dampen testosterone release," says psychologist David Geary, a co-author. The differing physiological effects of battling opponents from ingroups and outgroups "are similar to the testosterone challenge response found during male-male competition over mates and status in other species," he says. Harvard University primatologist Richard Wrangham says the findings from the study are "highly suggestive. ... The influence of prehistoric war on the biology of male brains looks critical to understanding the allure of violence."

Ready to Drill

A complete overhaul of the scientific drilling vessel *JOIDES Resolution* (JR) "has created a new and transformative science environment," says the ship's head of scientific operations, geochemist Mitchell Malone of Texas A&M University in College Station. The \$130 million, 3-year refurbishment, completed earlier this year in Singapore, increased lab space by 34%, Malone says. All lab equipment has been renovated or replaced.

Living quarters for the scientific crew of 60 are more comfortable, too. On the old JR, researchers stayed in four-bunk cabins, with eight people sharing a bathroom. Now there are two beds to a room, and baths have been doubled. Roommates are put on staggered 12-hour shifts so they can have the room to themselves on off hours.

The JR is the U.S. National Science Foundation-funded contribution to the 16-country Integrated Ocean Drilling Program, which probes the sea floor to study the deep biosphere, environmental change, and Earth's geodynamics. The ship called at Yokohama in early September to change crews and resupply. It is now drilling into rock at the Shatsky Rise, a Pacific plateau 1500 km east of Japan, seeking clues to the formation of such plateaus.

Fermi Award

Physicists Sig Hecker of Stanford University and John Goodenough of the University of Texas, Austin, will share this year's \$375,000 Enrico Fermi Award from the Department of Energy. Hecker, 65, is the former director of Los Alamos National Laboratory and an international expert



JOIDES in Yokohama.

CREDITS (TOP TO BOTTOM): LINDA A. CICERO/STANFORD NEWS SERVICE; COLORBLIND IMAGES; D. NORMILE/SCIENCE



North Korea's
unusual
new university

1610



Nuclear waste
debate flares
in Germany

1612



HUMAN EXPLORATION

Obama Facing Tough Decision on Whether to Keep Aiming for the Moon

Not since Richard Nixon sat in the Oval Office has the United States faced a more difficult decision about what to do with its space program. Last week, the chair of a presidential panel on human space flight told two congressional panels that NASA doesn't have enough money to carry out the current plan to build a big rocket to take humans back to the moon and that the United States should consider other destinations and launchers.

Many lawmakers oppose any major deviation from the plan, laid out by President George W. Bush in 2004, to build a base on the moon using a new launcher system called Constellation. But the White House, eager to put its own stamp on a long-term exploration effort, is drawn to other options described in the panel's executive summary released earlier this month (www.nasa.gov/offices/hsp/home/index.html). For President Barack Obama, who is expected to announce his space vision this fall, the challenge is to find a politically acceptable answer to the question of where NASA should send humans—and how.

The status quo is not a viable option, says Norman Augustine, the retired aerospace chief who chairs the committee set up this spring by the White House. The United States

could "continue the present program until, frankly, it falls off a cliff due to lack of money," he warned members of the House Science and Technology Committee during its hearing on 15 September. Staying the course, he explained, would require at least \$3 billion more a year, although a lunar landing would be delayed far beyond the original target of 2020.

The Augustine panel—which is still working on its final report—has offered the Administration a series of choices rather than a single recommendation. They range from adding more money to the current Constellation program—a family of launchers that eventually could take astronauts beyond low-Earth orbit—to a rocket derived from space shuttle technology. NASA could also contract with private companies to provide rides into orbit. As for where to go, the moon could remain the destination, or NASA could shoot for a more flexible approach that might allow humans to orbit an asteroid or martian moon before eventually landing on Mars.

There is tentative agreement on both ends of Pennsylvania Avenue that NASA should stick with the current plan to retire the three aging space shuttles by 2011 but prolong the life of the space station in orbit

from 2016 to 2020. To service the station during that interim, NASA would initially buy Russian Soyuz vehicles and then use either commercially developed launchers or a new NASA rocket.

A coalition of aerospace companies, labor unions, former NASA officials, and Republican and Democratic politicians say that there's nothing wrong with the Bush Administration's space vision that more money couldn't fix. Any alterations, they fear, would jeopardize the precarious support NASA now enjoys in Congress, they say, as well as thousands of skilled jobs. "There needs to be a compelling reason to scrap what we've invested our time and money in over the years," said Representative Bart Gordon (D-TN), chair of the House science committee.

Legislators fear that building a different launcher and picking a new destination might eventually cost more than the current plan, which has been in the works for several years. "I have no interest in buying a pig in a poke," says Gordon. So far, NASA has spent some \$8 billion on Constellation, and the space agency plans its first prototype test at the end of October. Former NASA Administrator Mike Griffin, who also testified before the House, came down strongly in favor of maintaining the Constellation-to-the-moon plan.

Sources close to NASA say that the new NASA administrator, Charles Bolden Jr., also favors the current plan. A former astronaut, Bolden was originally scheduled to testify as well but was dropped from the witness list because the Administration has yet to formulate a response to the Augustine options.

Bolden's stance could put him at odds with White House officials hoping for a more exciting destination than the moon, which Americans reached 40 years ago. Administration officials are also worried that Constellation's technical and financial troubles will grow in coming years.

Although Augustine refused to take sides despite pointed questioning at the hearings, he repeatedly cited the possibility of using commercial launchers and choosing a different destination. "The flexible path options are particularly interesting to me," Augustine told the Senate commerce and science committee on 16 September.

Rather than landing on the moon, which requires an expensive lander system, astro-

ILLUSTRATION: JOE SUTLIFE



Nutrition
and violence

1614



Listening in on
the very early universe

1617

nauts could rendezvous with an asteroid to test how to move such a body out of harm's way if it threatens Earth. Or humans on the asteroid-sized moons of Mars could teleoperate rovers on the martian surface. Those moons and asteroids exert only a fraction of the gravitational pull of a planet or Earth's moon and therefore require far less fuel to land on and leave. That's a key consideration in estimating costs.

The ultimate goal—not likely for 15 to 20 years—would be landing people on Mars. “There’s great merit to having some interim milestones along the way to Mars, where you can point to significant scientific and technological accomplishments,” Augustine noted. Although Bush’s vision included a string of interim steps, the committee in its public hearings found limited enthusiasm for an Apollo redux.

However, adding \$3 billion a year to NASA’s \$18 billion annual budget to carry out such missions—whether to the moon or elsewhere—doesn’t sit well with a lot of lawmakers. “This is no longer the era of Apollo and the Cold War, where the payoffs for advancing the space and moon agenda are entirely clear,” said Senator Jay Rockefeller (D-WV), who chairs the Senate science panel. “Our country does not necessarily have the resources to do everything we want to do.”

The debate was not supposed to begin in earnest until after the Augustine panel submitted its final report. But Augustine, to the irritation of Administration officials, insisted upon satisfying the panel’s mandated 90-day study period and released an executive summary in early September.

White House officials say they need to digest the full report before drawing up a

5-year budget plan. That task falls to the Office of Science and Technology Policy and the Office of Management and Budget, now hard at work. Their recommendation will then go to Obama, who is expected to announce a new policy by November.

“The president really has a major decision here,” said Senator Bill Nelson (D-FL), who flew on the space shuttle in 1985 and who played a key role in Obama’s selection of Bolden. “I believe [he] will make a bold stroke not unlike President Kennedy,” said Nelson, referring to Kennedy’s 1961 pledge to put a man on the moon by the end of the decade.

That announcement is expected to kick off a contentious debate next year in Congress. And Obama will need all of his political skills to convince both space supporters and deficit hawks that he’s on the right trajectory.

—ANDREW LAWLER

NATIONAL INSTITUTES OF HEALTH

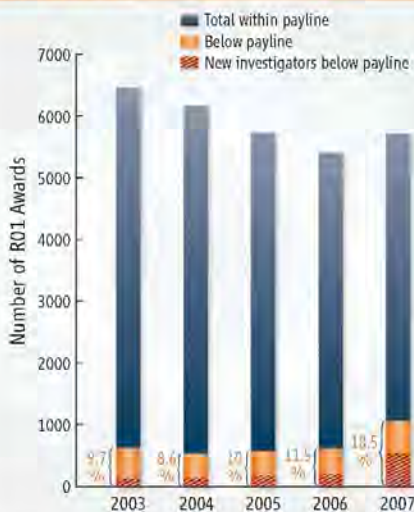
Grants ‘Below Payline’ Rise to Help New Investigators

A new analysis of the grantsmaking process at the National Institutes of Health (NIH) lifts the veil on how many grant proposals are funded even though they fall below a cutoff based on peer-review scores. The bottom line—at least 19% of NIH’s basic research portfolio is funded for reasons that go beyond quality—may stoke simmering concerns about the agency’s policy that favors young investigators.

The finding is part of a U.S. Government Accountability Office (GAO) report released this week that examined management practices at NIH’s 27 institutes and centers. One touchy question is how often they depart from “priority scores” assigned by peer-review panels. Institutes usually set a “payline” or minimum score that a proposal must receive to be funded. But they also fund proposals below that line, for reasons that include balancing the institute’s portfolio and giving new investigators a leg up.

Until this week, the NIH-wide numbers hadn’t been made public. The most surprising aspect of the GAO report, besides the overall number of exceptions, is its discovery of a sudden increase 2 years ago. In 2003, 625 of 6461 R01s, NIH’s basic research grant, fell below the quality cutoff. In 2007, the most recent year examined, the total had jumped to 1059 of 5715 awards (see graph).

NIH R01 AWARDS



Making exceptions. In 2007, 18.5% of funded NIH R01 grants missed the quality cutoff, up from 9.7% in 2003—much of the increase for new investigators.

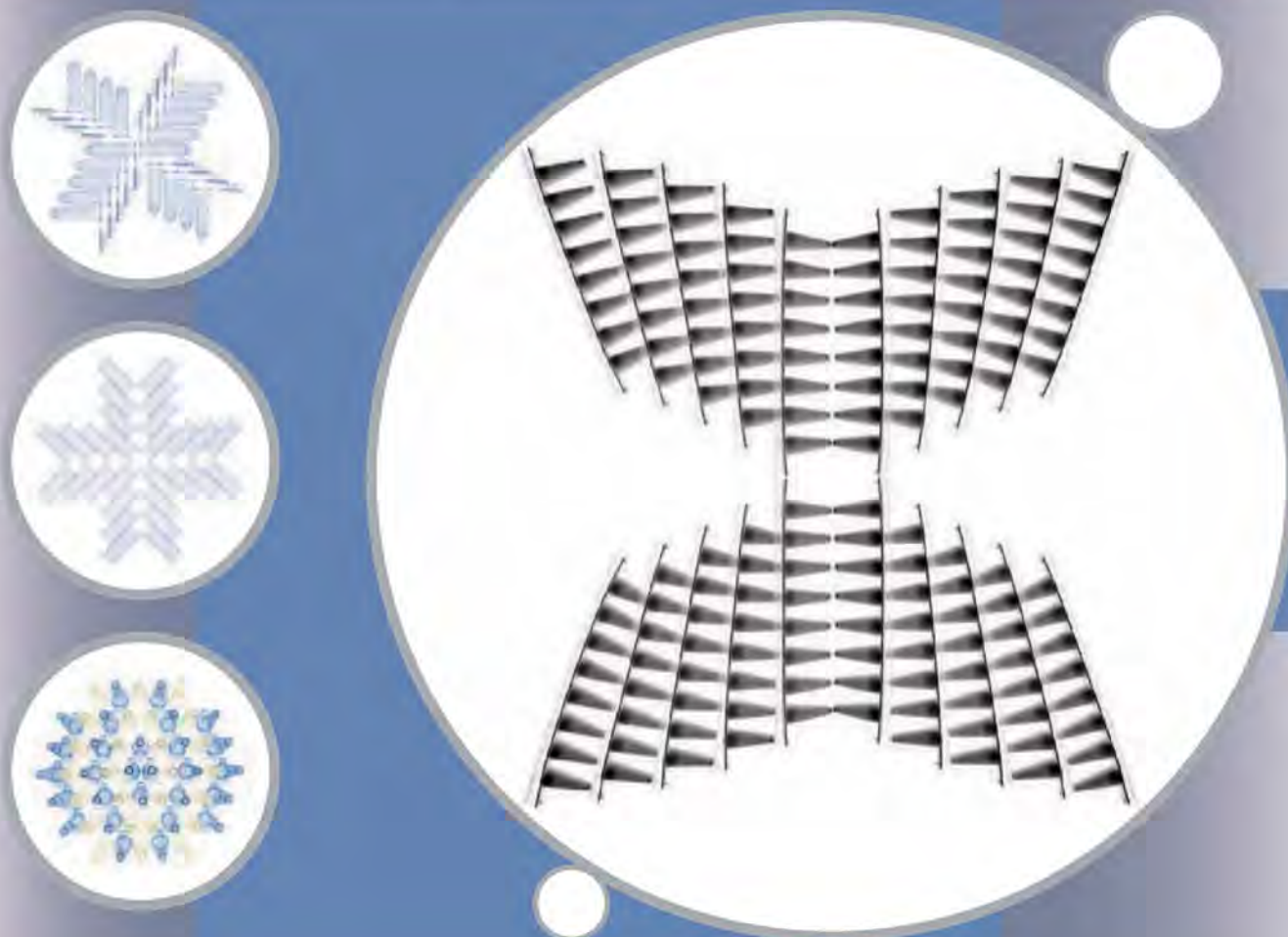
The GAO report refers to “a substantial increase,” but NIH says it is really nothing to be concerned about. The funded grants are all “reviewed, meritorious applications,” says Sally Rockey, NIH acting deputy director for extramural research. The recent rise, she

notes, is due almost entirely to NIH’s new policy favoring new investigators aimed at curbing a steady rise in the average age at which an investigator first receives an R01 (*Science*, 7 November 2008, p. 834).

Still, the data surprised one observer familiar with NIH’s grantsmaking process. “There will be people who will say, ‘What the hell’s going on here?’” notes molecular biologist Keith Yamamoto of the University of California, San Francisco, who for years has been involved in overhauling the peer-review system. As a staunch proponent of the new investigator policy, however, he’s comfortable with the rising number of exceptions.

Senator Charles Grassley (R-IA), who has also been investigating financial conflicts in medicine, requested the report after questions arose in 2007 about proposals with below-payline scores being funded by NIH’s environmental health institute. GAO recommends that the NIH director monitor such exceptions more closely, calling them “an area of potential risk because [institute] directors have latitude.” NIH officials disagree with that remedy, however, and wrote GAO that the institutes already document the reasons for their decisions.

—JOCELYN KAISER



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LIFE SCIENCES

A New Biology to Mend Society's Woes

When a National Academies panel was created last year to examine where to go next in life sciences, some thought it would focus on biomedicine—or merely ask for more money. So many science advocates were pleased last week when the panel called for a multidisciplinary initiative to address four major societal problems involving food, energy, the environment, and health. The report likens these goals to sending a man to the moon and the Human Genome Project.

"I think it's terrific," says Mary Clutter, former chief of the National Science Foundation's (NSF's) biology directorate and now a consultant. The emphasis on biofuels and crop production is welcome for a chronically

In the report, *A New Biology for the 21st Century*,* the 16-member panel found that biology has reached "an inflection point" where "many different disciplines" can come together to solve problems, says co-chair Phillip Sharp, a molecular biologist at the Massachusetts Institute of Technology (MIT) in Cambridge. This includes life scientists, physical scientists, mathematicians, and engineers.

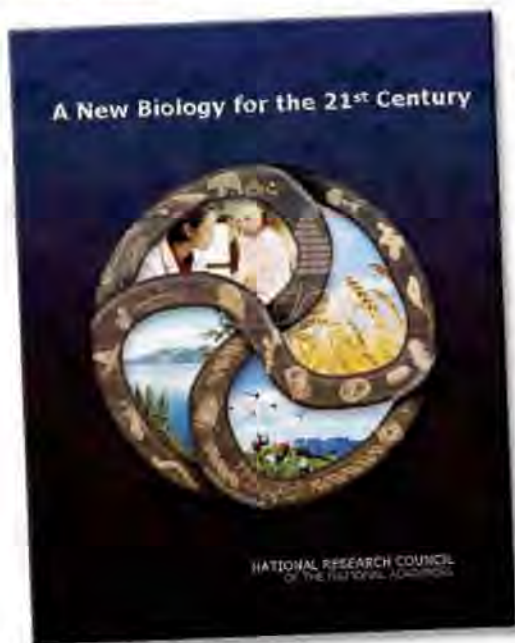
One program would aim to adapt food plants to any local growing conditions. A second would improve ecosystem monitoring and restoration. A third would combine crop research and microbial engineering to make biofuels a viable alternative to fossil fuels. And a fourth program would use personalized medicine to improve health care. Because the four challenges overlap—all involve complex systems, for example, and food production should not harm the environment—they "cannot be solved in isolation," says panelist Keith Yamamoto, a molecular biologist at the University of California, San Francisco.

The initiative should be funded in separate agencies but coordinated, according to the panel, and existing research funding should be expanded to accommodate at least a 10-year initiative. One possible model is the U.S. Global Change Research Program, says panelist Anthony Janetos of the University of Maryland, College Park. Although the report includes no price tag, its discussion of similar projects points to a total budget of at least \$2 billion a year.

Although several science advocacy groups praised the report, some privately expressed skepticism, noting that much of the research sounds familiar and lacks clear endpoints. Sharp argues that these areas are "not being pursued at a scale that will support our national needs." He also says an inter-agency initiative would help bridge agency-specific grants systems that deter researchers from crossing disciplines.

Others noted that the report seems unlikely to have the same impact as the *Gathering Storm*, which was requested by Congress and endorsed by industry groups. What's more, it comes during a recession. The panelists, however, who have already briefed congressional staffers and White House officials, are optimistic that their report will influence 2011 budgets, and they pledged to stay involved in fleshing out the details. The White House science office declined to comment.

—JOCELYN KAISER



Thinking big. The "new biology" could help boost crop production, improve biofuels, heal ecosystems, and personalize medicine, an expert panel says.

underfunded field, says Jeff Dangel of the University of North Carolina, Chapel Hill: "As a plant scientist, I'm delighted."

The advice comes from a panel funded by NSF, the National Institutes of Health, and the Department of Energy to examine how to build on the explosion of biological data from DNA sequencing and other efforts. It was also, in part, a response to *Rising Above the Gathering Storm*, a 2005 academies report that stimulated Congress to boost funding for physical sciences (*Science*, 12 December 2008, p. 1623).

*www.nap.edu/catalog.php?record_id=12764

ScienceNOW.org

From *Science's*
Online Daily News Site

Antplant Ants Are Never Satisfied

In tropical forests, certain types of trees serve as homes for ants, providing hollow stems or leaf pouches where the insects can live and raise their young. In return, the ants keep hungry herbivores at bay and occasionally kill surrounding vegetation, creating a clearing around the trees. Tropical biologists have now discovered that sometimes these ants branch out farther, invading other types of trees beyond the clearing. But are they out to destroy—or are they just trying to make new friends? <http://bit.ly/LsVGc>

And the Solar System's Coldest Spot Is ...

What's the coldest spot in the solar system? For now, that distinction belongs to permanently shadowed craters near the moon's south pole, according to the first results from the Lunar Reconnaissance Orbiter spacecraft announced this week at a NASA press conference. Shivering in at a mere 33 degrees above absolute zero, the regions are likely places to find deposits of water ice, a resource that would be in demand if astronauts ever live on the moon. <http://bit.ly/1I7f5l>

Gene Therapy Gives Monkeys Color Vision

Squirrel monkeys can now see your true colors, thanks to gene therapy. Researchers have given the color-blind primates full color vision as adults by injecting their eyes with a human gene. The result raises questions about how the brain understands color, and it could eventually lead to gene-therapy treatments for colorblindness and other visual disorders in humans. <http://bit.ly/3HDCAu>



Magnetized Gas Points to New Physics

It would be tough to stick it to your refrigerator, but an ultracold gas magnetizes itself just as do metals such as iron or nickel, a team of atomic physicists reports. That cool trick shows that the messy physics within solids can be modeled with pristine gases, the researchers say. But others are skeptical that the researchers have actually seen what they claim. <http://bit.ly/119g0V>

Read the full postings, comments, and more on sciencenow.sciencemag.org.

PROFILE: KIM CHIN-KYUNG

The Force Behind North Korea's New Science University

YANJI, CHINA—At the height of the Korean War, a scared 16-year-old boy made a promise as he lay wounded by shrapnel on a battlefield. “I said, ‘God, if you save my life, I will return this love to my enemy,’” recalls Kim Chin-Kyung, who was fighting for the south against the north. Six decades later, the 74-year-old businessman turned university administrator is keeping his word. Last week, Kim was appointed president of Pyongyang University of Science and Technology (PUST) at a ceremony in Pyongyang to commemorate completion of the \$35 million campus, which after 4 years of delays is expected to open in November to the crème de la crème of North Korea’s science graduate students.

Much of the credit for the feat belongs to Kim, who is modeling PUST after another improbable venture he heads: Yanbian University of Science and Technology (YUST) here in Yanji, capital of the Yanbian Korean Autonomous Prefecture in northeastern China. Kim has raised nearly all of the money for both universities from Christian groups in South Korea and the United States. The parallels between the two universities are striking—but PUST is freighted with symbolism. “PUST will be a bridge between the two Koreas,” says Park Chan-Mo, president of the National Research Foundation of Korea and one of three “founding committee chairs” of the new university. (The others are Kim and Malcolm Gillis, former president of Rice University in Houston, Texas.)

Its ambitions may be lofty, but PUST is starting out modestly. For the first year or so,

enrollment will be limited to 150 graduate students in three schools: information technology; industry and management; and agriculture, food, and life sciences. In late 2010 or early 2011, PUST officials say, the university will open two more schools—one for architecture and engineering and one for public health—and begin accepting undergraduates, with a target enrolment of 600 graduate and 2000 undergraduate students by 2012. Construction work has been completed on all academic facilities at PUST’s 100-hectare campus in southern Pyongyang’s Rakrang district. North Korea’s education ministry will handpick students; the incoming class has already been selected, Park says. Most revolutionary of all, in a country with a slick Intranet (*Science*, 17 September 2004, p. 1701) but a mere handful of closely guarded links to the outside world, PUST students and faculty are supposed to have unfettered Internet access.

PUST also aspires to be a research university. Administrators will gradually bring online an R&D center and a “Pyongyang Techno Park” open to foreign firms—primarily South Korean to start—that invest in the incubator. But research will be constrained by U.S. and European laws that proscribe export of certain scientific equipment and materials to North Korea.

Those limitations aside, officials on both sides of the divided peninsula have hailed PUST as a way to equip North Korea’s young elite with modern skills. “People who are trained now will play a major role in the country when it starts to change—and this is bound

to happen, sooner or later,” says Andrei Lankov, a North Korea expert at Kookmin University in Seoul, who is not affiliated with the venture.

Man on a mission

Kim does not have the typical resume of a university president. He took an English name, James, while studying divinity at Clifton Theological College in Bristol, U.K., in the early 1960s. (Clifton merged with two other evangelical colleges to form Trinity College Bristol in 1972.) In 1976, James and Grace, his wife, moved from South Korea to Florida, where they started out as wig importers and gradually built a small fashion empire that included women’s shoes and men’s clothing stores.

During a trip to China in 1987, James Kim was permitted to visit ethnic Korean enclaves in China’s northeast. While the people he encountered seemed happy, something was missing. “They had elementary and secondary schools, that was it. They needed higher education,” Kim says. “I never dreamed of building a university.” But it dawned on him that this was precisely what he had to do. After several rounds of negotiations with Chinese authorities, in 1988 Kim agreed to establish a 1-year vocational college in Yanji. He raised money from Christian groups in South Korea and the United States to supplement money he and Grace amassed from selling off their Florida businesses, and in 1992 YUST was founded on the hilltop site of what had been a cemetery, where Kim sometimes saw “children playing soccer with skulls.” The next year, in consultation with local authorities, Kim and his formidable fundraising operation helped convert YUST into a 4-year university that now has a student body of about 1800. Two hundred faculty members from 12 countries, along with their families, live in the dorms with the students and share meals. “We care for students like parents,” says Kim, who is often seen roaming the halls and starting conversations with students. During school breaks students perform social work, such as helping at orphanages and nursing homes.

Soon after YUST opened, North Korea began dispatching delegations to take the measure of the new university just across their northern border, and Kim began paying return visits, sometimes ferrying donations of food and clothing to North Korean orphanages. On one such trip in 1998, Kim, a dual citizen of South Korea and the United States, was accused of being an American spy and was imprisoned. At one point he was told he would



A promise kept. North Korea education official Keuk-Mahn Chon appoints Kim as PUST president at a 16 September ceremony.

CREDIT: NAMHO KIM/PUST



Love thy enemy. In 1998, Kim expected to die in prison in Pyongyang; now he's about to open a university there.

be executed, so he hurriedly penned a will and a pledge to donate his organs for medical research in Pyongyang. But Kim was released after 6 weeks in custody, and today he is one of the few foreigners with official permission from North Korea to reenter the country freely.

Soon after Kim's rehabilitation, officials from North Korea's education ministry resumed their pilgrimages to YUST and in early 2001, to Kim's astonishment, they invited him to create a similar venture in Pyongyang. When Kim floated the idea to his YUST backers, he got a rapturous response—and contributions poured in. As Kim and his flock began drawing up the blueprint for PUST, they based it largely on their experiences in Yanji, incorporating everything from YUST's curriculum and its technopark to the long hallways linking YUST's buildings to protect students from harsh winter winds. "YUST is a steppingstone to PUST in many ways," says Honghee Debbie Ko, a computer science professor at YUST and recent transplant from Florida.

As PUST's president, Kim has authority to appoint faculty and staff of any nationality. Although many of the first few dozen foreign faculty members are devout Christians, including Ko and others currently at YUST, administrators have assured North Korea's education ministry that religion will not enter the classroom. They had made a similar guarantee to China. All Chinese universities are owned by the state, and YUST is no exception: It is an autonomous college of Yanbian University, which provides the 16 credits of Communist theory, including Mao Zedong

thought, required for graduation in China. "We respect their system and culture. And we do not break the law," says Kim.

Whereas YUST's student body is largely drawn from China's ethnic Korean community—a tiny fraction of the country's population—North Korea, says Park, will be sending PUST the brightest grads of its top universities, including Kim Il Sung University and Kim Chaek University of Science and Technology, both in Pyongyang. Such high-level students will require top-notch faculty and a research environment, he says.

Few Western scientists have hands-on experience in North Korea; some say they hope PUST's opening will help usher in a new era of engagement. According to North Korea's central news agency, in a speech in Pyongyang last month the country's leader, Kim Jong Il, stated that "nationalistic self-respect does not conflict with receiving advanced technology from other countries" and called on his citizens to "plant our feet on North Korean land and look around the world, learning what we can learn and taking in what we can take in." PUST's opening "underscores the seriousness of recent statements attributed to Chairman Kim," says Stuart Thorson, a political scientist at Syracuse University in New York state who leads a U.S.-North Korea exchange that helped Kim Chaek create a digital library. "I hope that this bodes well for other academic science cooperation efforts," he says.

No one expects an easy road ahead for PUST. Even the dedication ceremony on 16 September was touch-and-go to the last moment. Fuming over the North's failure to apologize for the release of water from a dam earlier this month that killed six South Koreans, South Korea's Ministry of Unification initially forbade its citizens to attend the ceremony. After appeals from Park and others, the ministry relented and a few days before the ceremony, the ministry gave permission for 20 South Koreans to go. Another 90 dignitaries from seven other countries received North Korean visas.

The experiment is planned to run for at least 50 years: That's the term of the lease North Korea has granted to PUST's administrator, the Northeast Asia Foundation for Education and Culture, a nonprofit with offices in Seoul; Los Angeles, California; Sydney, Australia; and Toronto, Canada. The foundation, which raised the funds for PUST's construction, must come up with another \$6 million a year in running costs. Kim doesn't anticipate that being a problem—and no one is about to doubt him. After all, says Ko, "many people think it's a miracle to have gotten this far." —RICHARD STONE

ScienceInsider

From the Science Policy Blog



Chinese Premier Hu Jintao told delegates at a special session on climate change at the United Nations that **China would cut greenhouse emissions** relative to economic growth by a "notable margin" by 2020, below 2005 levels. He declined to put a figure on the pledge, though he promised to continue "vigorous" development of green power.

In a flurry of developments on **swine flu preparations**, the Obama Administration said vaccine delivery would begin in the first week of October and announced a plan to share vaccine with developing countries, but a study found that young children will likely need two shots for adequate protection.

A new report highlighted the possibility of producing power using **underground coal gasification**, which offers commercial and climate benefits.

The National Institutes of Health has set up a Web site where NIH-funded scientists can fill out a form requesting approval for the use of particular **human embryonic stem cell lines**, and Director Francis Collins established a task force to advise him on which lines meet new guidelines to qualify for federal funding.

European Union Commission President José Manuel Barroso has proposed **new top-level science positions** within the organization, including a science adviser and a commissioner for climate action.

A biomedical engineer from Stanford University and a climate scientist at Cornell University joined an Insider conversation on how policymakers could make it easier for **young scientists** early in their careers.

In an interview with Insider, the first president of the new **National Research Foundation of Korea** said his organization wants to promote "more creative and higher risk projects."

For more science policy news, visit blogs.sciencemag.org/scienceinsider.



Nuclear Trojan horse? Protesters at a rally in Berlin claimed that Angela Merkel's party would undo the country's phase-out of nuclear power.

GERMANY

Election Heats Up Nuclear Debate

BERLIN—A nearly 3-decade-old telex message regarding the scientific evaluation of a disposal site for highly radioactive nuclear waste in Germany has become a prominent issue in the campaign leading up to Sunday's national elections. The telex has sparked charges that scientists in the 1980s bowed to political pressure, and it has heated up the long-simmering debate about the future of nuclear power in Germany.

For both political and scientific reasons, nuclear waste experts say, Germany needs to redo its hunt for a high-level waste repository. "We have to start a new search to determine whether there is a better alternative or not," says Karl-Heinz Lux of the Clausthal University of Technology in Germany. A steady stream of revelations about problems at one of the country's repositories for lower-level waste, which had been managed by a prominent research center, has added potency to the issue.

The debate over storage of high-level wastes echoes the decades-long controversy in the United States over the Yucca Mountain nuclear waste disposal site, which was defunded by the Obama Administration earlier this year (*Science*, 20 March, p. 1557). There, too, politics drove the selection of a single, sparsely populated site as a potential repository. In both cases, the perception that politics, not science, drove the site choice has made the fight for public acceptance much harder, says Gerhard Jentzsch, a geologist at Friedrich Schiller University of Jena in Germany.

Nuclear power faces widespread skepticism among Germans, in part fueled by memories of the 1986 Chernobyl disaster. In 2002, the country's parliament passed a law mandating

the shutdown of the country's existing nuclear plants by 2022. Current Chancellor Angela Merkel has so far accepted that policy and officially all five of Germany's main parties say they will abide by the phase-out, but nuclear energy opponents fear that after the 27 September election, Merkel's Christian Democrats and their preferred coalition partner, the Free Democrats, will extend or scrap the deadline. Earlier this month, tens of thousands of protesters marched through the streets of Berlin to demonstrate support for the moratorium.

Finding a place to safely dispose of the country's nuclear waste has been the hottest topic. In 1977, the government proposed a large salt dome near the border with what was then East Germany. Located by a village called Gorleben, the site has been controversial from the start, attracting protests every year when waste is transported to a temporary storage facility at the site.

Among the concerns are that the clay layers covering the dome are too thin in some spots to adequately protect the salt deposits from leaching water. And geologists disagree on whether a salt deposit is the country's best option for the most radioactive nuclear waste.



Out of sites? Germany may reconsider this planned waste disposal facility near Gorleben.

"High-level nuclear waste produces heat, which can draw water out of the salt," says Jentzsch, who suggests clay deposits may be a better alternative.

Election-driven politics have now led to new questions about Gorleben. Earlier this month, Environment Minister Sigmar Gabriel confirmed the discovery of a telex message sent in 1983 by government officials to scientists evaluating the site as a potential repository. The message seems to substantiate media charges from earlier this year that scientists were pressured by government officials to alter their report. In a draft report, the researchers had said the site was adequate but should be compared with other possible sites. The final report deleted the recommendation for a comparison.

Gabriel, a member of the center-left Social Democrats, called the telegram a full-blown scandal. An aide to Merkel initially dismissed its importance, but the chancellor herself said a few days later that she had asked for an investigation into the matter. Officially, Merkel and her party stand by their position that Gorleben is an appropriate site.

Although it has been colored by election politics, Lux says, the public debate about Gorleben is necessary. "There is no way around the fact that we have to find some final storage site," he says. Whether politicians decide to continue with the phase-out or not, "the waste is there and has to be dealt with." The only way to win public support is to start a new search process that would investigate possible alternatives, he says: "Without a comparison, we can't go further with Gorleben."

Gorleben's critics have been strengthened by revelations about another salt-based nuclear waste dump nearby. Called Asse II, it has been used since the 1960s to dispose of waste from several of Germany's research institutes. Government authorities took over the site in January after the research center that had been administering it, the Helmholtz Center Munich, failed to inform authorities that brine had been leaching from the complex. Since then, investigators have found evidence that more and higher-level waste than allowed was deposited at the site. Adding a grisly element to the furor, news surfaced last week that the partial cremated remains of two workers killed in a 1975 accident at a nuclear power plant might also have been buried there. Environment Minister Gabriel has estimated that the cleanup and closing of the site could cost as much as €4 billion. "Asse is a catastrophe, both politically and scientifically," Lux says. "It will take years to rebuild the trust that has been lost in the process."

—GRETCHEN VOGEL

CREDITS (TOP TO BOTTOM): PERCY VOGEL; CHRISTIAN CHARIUS/REUTERS/LANDOV

ASTRONOMY

Who Will Pay for China's Planned X-ray Satellite?

BEIJING—After spending nearly 2 decades developing China's first space-based observatory, Li Típei now fears that the project may never get off the ground. The Hard X-ray Modulation Telescope (HXMT) mission is scheduled for launch next year, but with the clock running down, *Science* has learned that no government agency has stepped forward to pay the estimated \$146 million to build the satellite—putting the mission in jeopardy. “It would be a shame for the Chinese scientific community if the project dies prematurely,” says Li, an astrophysicist and chief mission scientist at the Chinese Academy of Sciences Institute of High Energy Physics (IHEP) and Tsinghua University here.

To avert that possibility, Li and supporters are appealing to the highest level of government: In May, 15 academicians petitioned the State Council, and last month, the most senior signatory, 95-year-old nuclear physicist He Zehui, sent a personal note to Premier Wen Jiabao, who heads China's cabinet. “There are not many opportunities in the history of science for making original contributions using truly innovative methods,” she wrote. Astrophysicists are hoping for an 11th hour intervention from Wen to save the mission.

The idea for HXMT was born in 1992, when Li and IHEP astrophysicist Wu Mei developed a mathematical method for reconstructing images from spatial data collected by satellite-borne hard x-ray and gamma-ray instruments. Based on their method they proposed HXMT, a telescope in low-Earth orbit that would operate in a wide-field mode to carry out an all-sky survey in the hard x-ray energy range of 20 to 200 kiloelectron volts (keV)—where it would catalog objects such as x-ray binary systems and supermassive black holes—and in a pointing mode to observe known sources and study their variability.

Because photons with energies above a few tens of keV cannot be focused, imaging for hard x-ray and gamma-ray observations employs a technique called aperture modulation. Imagers aboard the European Space Agency's International Gamma-Ray Astrophysics Laboratory (Integral) and NASA's SWIFT satellite, both now in orbit, use spatial modulation. In this technique, a thick metal plate with a complex two-dimensional pattern—a “coded-aperture mask”—is placed in front of a detector array. X-ray and gamma-ray sources project shadows of the

aperture mask onto the detector plane, from which scientists can reconstruct the position, spectrum, and variability of each source over time, explains Pietro Ubertini of the Institute of Space Astrophysics in Rome, who is principal investigator of Integral's imager.

HXMT, on the other hand, uses a technique called temporal aperture modulation. A “slat collimator” made of parallel metal plates is placed over a flat detector and limits the field of view directly overhead. In survey mode, the collimator would rotate around an axis perpendicular to the detector plane, casting a time-variable shadow onto the detector. Source images are obtained using the sophisticated math Li and Wu devised. HXMT “is a good and simple technology,” says Ubertini, and its imaging sensitivity should be comparable to the more complex imagers aboard Integral and Swift.

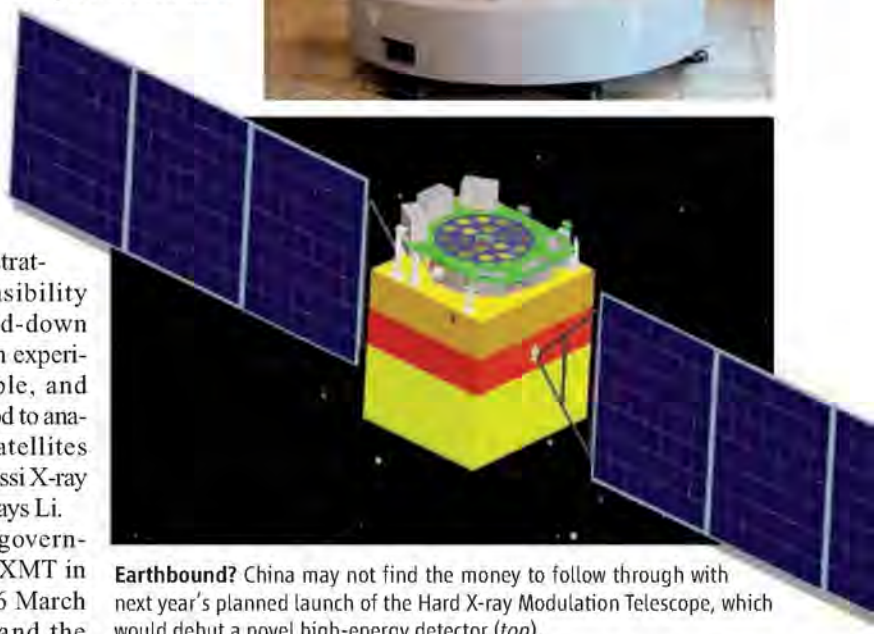
At first, many scientists were skeptical that HXMT would work. It took Li's group almost 15 years to convince critics by demonstrating HXMT's feasibility through a scaled-down model in a balloon experiment, for example, and applying the method to analyze data from satellites such as NASA's Rossi X-ray Timing Explorer, says Li.

The Chinese government approved HXMT in 2007 (*Science*, 16 March 2007, p. 1481) and the State Administration of Science Technology and Industry for National Defense (SASTIND)—the agency in charge of civilian space programs—ranked the mission the highest priority after human space flight and lunar exploration in the country's first-ever 5-year plan for space science.

But the mission is now in trouble. Li has learned that SASTIND is running out of funds for the current budget period ending in 2010. The finance ministry will not supplement the agency's coffers because ministry officials expect the science academy to step in and provide support using its special fund for innovation. Li says the problem

reflects a lack of coordination in China's civilian space program.

A launch delay could prove costly. NASA's Nuclear Spectroscopic Telescope Array, slated for launch in September 2011, will take much sharper hard x-ray images



Earthbound? China may not find the money to follow through with next year's planned launch of the Hard X-ray Modulation Telescope, which would debut a novel high-energy detector (top).

than HXMT in the pointing mode, says Joachim Trümper, a retired astrophysicist at the Max Planck Institute for Extraterrestrial Physics in Tübingen, Germany, but he says there is still strong justification to get HXMT into orbit soon. Jonathan Grindlay, an astrophysicist at Harvard University, agrees because “no other wide-field imaging hard x-ray satellite missions are planned” over the next 5 years. Li and others are pinning their hopes on Wen. In China, big projects have always depended more on having a high-level patron than on scientific merit alone.

—HAO XIN

The Theory? Diet Causes Violence. The Lab? Prison.

In a more ambitious study than any before, psychologist Bernard Gesch is leading a research team hoping to replicate controversial results showing that nutritional supplements can reduce violence among prisoners

FALKIRK, SCOTLAND—The officer tenses slightly as he approaches a junction in the corridors that connect buildings in the Polmont prison compound. Two groups of prisoners are about to converge.

Her Majesty's Young Offenders Institution Polmont is Scotland's most violent prison—based on its record of assaults—but a peaceful atmosphere usually prevails. The officers seem to be on good terms with their charges—about 700 young men between the ages of 16 and 21, many of whom will go on to adult prisons to serve life sentences. When the violence happens, it erupts in a flash, and typically in hot spots like this junction where groups of prisoners encounter each other. The officers usually intervene well before serious damage is done. But not always. There have been stabbings, and some weeks ago a prisoner was sent to the hospital after a kettle of boiling water was thrown in his face.

The boisterous young men arrive from opposite directions, each led by an officer. Both prisoner groups are from Monro level 4, the ward for those at the highest risk for harm. Some of them are targeted in gang-related feuds. Some carry the dangerous stigma of being sex offenders, referred to as “beasts” by the others. The prison carefully coordinates everyone's movements with a computer system similar to air traffic control. The two lines merge and file past without incident.

Violence is what landed many of these young men in prison, some for crimes so horrible that they shocked the nation. But violent behavior also brought another group of people to Polmont: a team of scientists.

Online

sciencemag.org

S Podcast interview and reporter's notebook.

At lunchtime, prisoners emerge from their cells and begin gathering at a steaming buffet cart. After piling their trays with a typical meal—bread, sausage, and soup—the prisoners stream by a table staffed by the scientists, all wearing identical bright pink shirts that set them apart from the prison staff.

One of the young inmates pauses, setting his tray on the table. Lisa Gilmour, a psychologist, finds his name on a list of prisoners who have volunteered for the study. Next to his name is a code that corresponds to a sachet containing his allotments of pills. She gives them to the prisoner and watches as he pops them in his mouth and chases them down with water.

Those pills were either a standard supplement of vitamins, minerals, and essential fatty acids, or starch placebo pills designed to look and taste just like the supplement. The prisoner has no way of knowing which it was, and neither does Gilmour, because an independent third party randomly assigned the prisoners to the two groups. The officers, who also have no idea which prisoners are in the treatment or control groups, monitor their charges' behavior as usual, recording every infraction from threatening language to physical assault. The goal of this double-blind trial is to definitively answer a question that has bedeviled behavioral science for a century: Are nutritional imbalances a cause of violence?

Watching silently in the background is the study's

leader, Bernard Gesch, a nutrition and criminology researcher at the University of Oxford. To most people outside Gesch's field, his hypothesis—that, simply stated, improving diet helps prevent fights—sounds crazy. But he has evidence to back the claim. In 2002, he published the results of a double-blind trial with more than 200 young prisoners in Aylesbury, England. Those who received nutrient supplements committed significantly fewer violent offenses compared with the placebo group.

After years of wooing funding bodies and fighting for access to prison populations, Gesch now has an even more ambitious study approved and bankrolled. Impressed by the strength of his earlier results and the rigor of his experimental design, the U.K.'s Wellcome Trust announced last year that it would provide \$2.3 million for a nutritional supplement trial involving more than 1000 prisoners from Polmont and two other U.K. prisons. The 3-year trial, which started this spring, includes blood chemistry analysis and a battery of computer-based behavioral and cognitive tests designed to address the question that the earlier study could not: If a balanced diet does stem violence, how exactly does it do so?

It appears that the nutrition-violence hypothesis is gaining momentum. A study within the Dutch prison service, similar to Gesch's 2002 study, has also recently found that supplements reduce violence. (As *Science* went to press, that study was in review for publication.) If Gesch's larger study confirms the effect, “policies



Diet plan. Bernard Gesch suggests supplements can stem violence.

CREDITS (TOP TO BOTTOM): J. BOHANNON/SCIENCE; COURTESY OF BERNARD GESCH

Good behavior? Polmont prison (left) is home to violent offenders, but nutritional supplements may help keep the peace.

will have to change,” predicts Stephen Schoenthaler, a nutrition and criminology researcher at California State University, Stanislaus, in Turlock. But that may be an optimistic view. Decades of studies by Schoenthaler and others have supported a connection between nutrition and violence, but for a variety of reasons—some scientific, others political—it hasn’t yet translated into policy.

You are what you eat

“The idea of a link between diet and antisocial behavior is not new,” says Gesch. As far back as 1892, the Italian criminologist Cesare Lombroso reported that many bomb-throwing terrorists suffered from pellagra—malnutrition due to a corn-based diet deficient in vitamin B-3—and proposed a connection. But nutrition-violence theories didn’t gain traction until chemistry and physiology began to reveal molecules in food that could regulate hormones and neurotransmitters—and thus conceivably behavior. By the 1960s, some argued that nutrition can not only cause behavioral problems but cure them; Nobel Prize-winning chemist Linus Pauling made the case for “orthomolecular psychiatry” in *Science* (19 April 1968, p. 265), defining it as “the treatment of mental disease by the provision of the optimum molecular environment for the mind.” According to Pauling, psychological disorders as severe as depression and schizophrenia could be fully treated with the right balance of vitamins and micronutrients.

Pauling’s proclamation symbolizes a problem in this area of behavioral research. “This field has seen a lot of exaggerated claims and not enough solid placebo-controlled research,” says Eugene Arnold, a psychiatrist and former director of the Nisonger Center at Ohio State University, Columbus. Studies have shown that “there clearly is a connection” between nutrients and behavioral disorders—for example, between nutrition and depression—but rigorous research has been the exception, he says. Most studies of the effects of nutrition on antisocial behavior are dismissed because of poor experimental design. And Arnold notes that misleading claims by the booming nutrient supplement industry have brought the taint of pseudoscience to those studying diet and behavior. “Even good scientists in this field have been treated as guilty by association,” he says.

Into this skeptical atmosphere entered Gesch, who certainly didn’t see nutrition or behavioral research on his horizon when he

went to university. “I trained as a physicist, but all the job prospects seemed to be in weapons,” he says. “I wanted to make a positive difference, so I went into social work.” In the mid-1980s, while working with young offenders in Cumbria, England, Gesch stumbled upon a simple but surprisingly effective strategy. “I invited them over for meals,” he says. “We cooked and ate together around a table like a family.” The goal was to get the young offenders to open up and share crucial information, such as the troubles in their family and school environments. Gesch says the youngsters transformed, becoming healthier and often abandoning the antisocial behaviors that had gotten them into trouble. He began to believe that shedding their scattershot diets of junk food was central to the behavioral shift, perhaps even more so than the family-like socializing.

myself hoarse,” he recalls with a laugh. The prisoners wouldn’t listen to him.

Gesch switched to a subtler tactic. “I asked around to find out who the ‘daddy’ was, the biggest, toughest guy around,” he says. A one-on-one meeting allowed Gesch to make his case. “I just explained that the study was completely in their own interest, and that it had nothing to do with the prison staff or the government,” he says. Once that prisoner signed on, 231 others voluntarily took part over the course of the 2-year study.

The results, published in 2002 in *The British Journal of Psychiatry*, revealed a significant effect: Prisoners given nutritional supplements committed 35% fewer violent incidences than those given the placebo. Gesch braced himself for a wave of doubt and criticism, but “the reception was surprisingly



On the menu. A typical meal at Polmont prison.

Over the next decade, diet and behavior became Gesch’s obsession. He founded a program to handle dietary education as part of criminal sentencing. He also created a charity, called Natural Justice, dedicated to researching the links between nutrition and criminal behavior and getting those insights translated into policy. In 1995, eager to rigorously test his idea, the then-36-year-old stood before hundreds of convicts in Aylesbury prison. The governor had agreed to let him run a double-blind study with nutritional supplements, but Gesch would have to persuade the prisoners to volunteer himself.

Gesch has piercing blue eyes and a neat crop of blond hair that tends to stand up like a cock’s comb as the day wears on. “I yelled

positive. Even the press treated us kindly,” he recalls. “There was clearly something there,” says Stephen Wong, a veteran criminal psychologist and visiting scholar at the Institute of Mental Health in Nottingham, U.K. “It needed to be replicated.”

Easier said than done. Getting permission to run a ramped-up version of the 2002 study in U.K. prisons required “years of lobbying,” says John Stein, a physiologist at the University of Oxford who is co-leading the current trial with Gesch. The reason, says David Ramsbothom, former chief inspector of the U.K. prison service, is “an enormous amount of resistance to any effort to improve prisons, in part because of simple-minded, ‘get tough on crime’ politics.”

But once the prison system permissions were secured, Gesch's grant application was approved by the Wellcome Trust in a matter of months. "We are all used to nutritional guidelines for our physical health, but this study could lead to revisions taking into account our mental health as well," announced Wellcome Trust Director Mark Walport.

The recipe for violence

Polmont's prisoners universally complain that meals are neither tasty nor fresh, and it's no wonder why. The food budget amounts to a few dollars per prisoner per day. And by the time it travels from the central kitchen facility, through the layers of security and up to each ward's dining area, foods such as fried potatoes are lukewarm and limp. Still, the prison governor, Derek McGill, says he never suspected that the prison food itself might be a cause of violence.

There are nearly as many theories for how nutrition affects behavior as there are nutrients in the body. For example, Adrian Raine, a psychologist at the University of Pennsylvania, is testing whether supplements of omega-3 fatty acids in particular can reduce antisocial behavior by helping young brains mature properly. Stein also proposes a role for omega-3's, noting that these acids are required in large amounts by Magna cells, a type of neuron crucial for attention and impulse control. Other nutrition-violence theories look to the vitamin B complex, which is crucial for everything from brain tissue maintenance to learning. Gesch and Stein hope that data from the study's blood sampling and behavioral testing will ultimately reveal which of more than two dozen nutrients—interacting with as many behavioral traits—makes a difference in violent behavior (see table, above).

They don't expect a simple answer. "Nutrition is about balance," says Gesch. "It's not like pharmacology." But even if the biochemistry of violent behavior turns out to be too complex to tease apart from the data, some

key insights may emerge. "Control of impulsivity may turn out to be very important," notes Stein. For example, a nutritional imbalance could suppress the ability to resist punching someone in the face in spite of strong emotions of fear or anger. If so, then prisoners who receive the nutritional supplements should do better than the placebo group on an impulsivity "stop-go" test—challenging prisoners to respond to "go" signs as quickly as possible while also heeding "stop" signs—that Gesch's team is administering before and after treatment.

One of the subjects in the study proposes a

of a connection between diet and violence—at least for prison populations. But even if it does, the debate over what to do with that knowledge is just getting started.

For some, the answer is already clear. "The [nutrition-violence] effect is obviously real, and it has been researched for 30 years," says Iver Mysterud, a behavioral psychologist at the University of Oslo in Norway. "The policy implications are obvious: Get rid of sugar and highly processed foods, improve the diet," and for prisoners with nutrient imbalances, "give [them] supplements with minerals, vitamins, and fatty acids."

Others are withholding judgment until the new data are in. "I'm skeptical, mainly because so many other assertions of vitamins on health and well-being have been proved wrong," says Randy Nelson, a neuroscientist at Ohio State University, Columbus, who specializes in the mechanisms of aggression. "However, the study design is very good and the preliminary data seem compelling." If prison violence can be prevented through diet, then "government agencies ought to put this into policy actions as soon as possible."

Why stop at prisons? If the nutrition-violence effect is confirmed with prisoners, could poor diet explain some of the violence and antisocial behavior in schools, or even in neighborhoods? Many researchers have argued this, but the link may not hold for the wider community, says Mysterud. Only a double-blind nutrition study in a community setting could settle that. Some are already under way, such as Raine's study of omega-3 supplements with children in Singapore and Philadelphia, Pennsylvania, with plans for another in Mauritius.

But Gesch and others stress that improving diet can be only part of the answer to violence and antisocial behavior. "Nutrition sounds like a silver bullet," says Wong. "But crime control has no simple solution."

—JOHN BOHANNON

DIET OF DISAFFECTION: NUTRIENT INTAKES FROM A SAMPLE OF DISADVANTAGED YOUNG PEOPLE

Nutrient	Percentage getting adequate intakes	Possible effects of low intakes on the brain
B-12 Cobalamin	94%	Pernicious anemia. Spinal cord damage. Raised homocysteine; this has been linked to cvs disease and hostility.
B-6 Pyridoxine	83%	Cofactor for conversion of tryptophan to serotonin (5HT) and regulation of homocysteine. Depression. Alzheimer's.
B-1 Thiamin	61%	'Dry beriberi': peripheral neuropathy, Wernicke's and Korsakoff's encephalopathy. Reduced learning ability associated with impaired hippocampal neurogenesis in animal models.
B-2 Riboflavin	33%	Cofactor in electron transport chain, energy metabolism, reduces ischemic brain injury.
Iodine	33%	Thyroid hormones—low intake of iodine is the commonest cause of mental deficiency worldwide
Folic acid	28%	Methylation agent in synthesis of serotonin. Low intakes are associated with depression and raised homocysteine.
Zinc	28%	Found in over 100 enzymes, affecting membrane structure, neurogenesis, neurotransmitters, fatty acid metabolism. Low zinc intakes have been associated with ADHD and criminality.
Calcium	28%	Neural hyperexcitability, paresthesia, impulsivity.
Iron	22%	Anemia. Also required for dopamine synthesis. Low iron is associated with impaired cognitive development in humans and aggression in animal studies.
Magnesium	17%	Involved in glycolysis and cerebral blood flow. Low intakes are associated with hyperexcitability and in animal studies with the severity of behavioral deficits.
Selenium	0%	Low intakes are associated with reduced cognitive function.
Omega-3 from fish	0%	Impaired attention, impulsivity, reduced memory, impaired cognition, depression, excess inflammation

similar hypothesis himself. "It comes down to a moment—you can hit someone or just walk away," says Craig, a towering 19-year-old with gang tattoos who is serving a 9-year sentence for culpable homicide. "And diet definitely makes a difference." He was one of several prisoners who shared their perspective on prison food and violence with *Science* (see the reporter's notebook online).

So far, the scientists working in Polmont have experienced violence themselves only once. One of the prisoners pulled out a plastic knife and threatened one of the researchers out of frustration. "He wanted his pills immediately," says Gesch. No one was harmed.

No simple solutions

Criminology researchers agree that Gesch and Stein's study should settle the question



Wired up. Low-band antennas of the Low Frequency Array (LOFAR).

ASTRONOMY

Exotic Telescopes Prepare to Probe Era of First Stars and Galaxies

Radio telescopes that substitute antenna arrays for dishes are gearing up to peer to the brink of the billion-year "dark ages" that followed the big bang

All this year, strange structures have been sprouting in the fields of northern Holland. Low gray boxes and what appear squat flagpoles held up by guy wires cluster in geometric patterns that look like landing sites for alien spacecraft. Their real purpose is only slightly less otherworldly: They are components of a giant radio telescope gearing up to probe the early history of the universe. With it and similar instruments, astronomers hope to peer back in time to when some of the earliest stars flared into life, and beyond that into the unexplored "dark age" of the cosmos.

The Low Frequency Array (LOFAR) is the largest of a new breed of telescope that will observe the sky via long-wavelength radio waves. Unlike conventional radio telescopes—huge movable dishes that point in one direction at a time—these new scopes are made of simple cheap antennas that pick up signals from all directions and then use sophisticated digital signal processing to "steer" a beam at the desired patch of sky. In fact, such a telescope can look at many parts of the sky at once, carving the received signal into multiple beams. "The antennas are extremely simple, but there is a lot of technology behind them," says Michiel van Haarlem, LOFAR's managing director. Similar instruments are either starting work or under construction in China, Australia, and the United States.

These versatile new scopes can survey and catalog the low-frequency sky, monitor fast-changing radio sources, study the sun and space weather, and track ultrahigh-energy cosmic rays as they hit Earth's atmosphere. But the goal that has scientists buzzing is the prospect of venturing into cosmology's terra incognita. The time from the release of the cosmic microwave background (CMB) radiation 400,000 years after the big bang until some 850 million years later, when the super-bright galaxies known as quasars became visible, is a closed book to cosmologists. This is a critical period of the universe's development, during which it evolved from a near-uniform cloud of neutral hydrogen gas into a gallery of stars, galaxies, and clusters of galaxies.

Cosmologists can only simulate what might have happened during this time because they have no data. "Simulations can get things evolved," says Michael Garrett, director of ASTRON, the Netherlands Institute for Radio Astronomy. This ignorance leaves a raft of questions. What were the first luminous objects like, and when did they form? Did large galaxies emerge fully formed from the primordial gas clouds, or did minigalaxies merge to make larger ones? And what, during that unseen period, caused the neutral hydrogen that emerged from the big bang to become ionized again? This era "is a tremendous

potential source of information," says Martin Rees, a theorist at the University of Cambridge and Britain's Astronomer Royal.

The creators of LOFAR and its kind are confident they can at least begin to answer these questions. If they succeed, similar but more powerful telescopes will soon follow. Many in the field liken it to the early days of studying the CMB. "The CMB produced several Nobel Prizes. I'd be surprised if [this] didn't do the same," says Garrett.

Into the dark

During the early millennia following the big bang, the universe was a hot, roiling fireball of subatomic particles and photons. Within 400,000 years, it had cooled enough for protons to pair up with electrons and form neutral hydrogen atoms, an era known as cosmic recombination. Neutral hydrogen could not absorb the low-energy photons that then pervaded the universe, and so space became transparent. Those photons—the CMB—are still flying through space and provide a snapshot of that moment in the universe's history. After recombination, things went quiet for a long time because there were no bright sources of light, just a diffuse, almost featureless cloud of hydrogen. "It's one part of cosmic time we don't have any information on," says Garrett.

That quiet gaseous state did not last. Gravity began working very slowly on slight variations in density in the gas cloud, pulling the matter in the denser regions closer together. Theorists believe the major player in this process was dark matter, the unknown substance thought to make up 85% of the universe's mass. Once you get clumps of dark matter as big as 100,000 solar masses, simulations suggest, stars will begin to form within them. According to some models, the first

stars may have turned on just 30 million years after the big bang, when the universe was less than 0.25% of its current age.

As the universe continued to evolve, the dark matter clumps got larger and encouraged the growth of galaxies and galaxy clusters. Theorists once thought that the hydrogen gas outside these dark-matter clumps, the intergalactic medium, would remain undisturbed, but observations of the IGM show that it has been ionized as far back as we can see, to when the universe was 850 million years old. So something in the era of the first stars and galaxies shone brightly enough to ionize all the hydrogen in the universe. Suspects include so-called population III stars, stellar giants that burned bright and fast in the early universe; some sort of mini-quasars; or even something more exotic such as decaying dark matter. This “epoch of reionization” (EOR) is now one of the main targets of LOFAR and similar instruments. “We want to understand when the first sources turned on, how they formed and where, and how structures formed on a cosmological scale,” says theorist Avery Meiksin of the Royal Observatory Edinburgh in the United Kingdom.

Stars and galaxies of that era are too faint for us to see today, but the new telescopes are not looking for starlight. Instead, they aim to detect a subtle difference between neutral hydrogen and ionized hydrogen. Both electrons and protons have a quality referred to as spin, and when they are combined in a hydrogen atom, the two spins can be either parallel or antiparallel. The parallel state has a slightly higher energy than antiparallel, so when the atom flips from the former to the latter, it emits a photon with a wavelength of 21 centimeters. Similarly, absorbing a 21-cm photon will flip the atom from antiparallel to parallel.

Ionized hydrogen, which has no electrons, neither emits nor absorbs 21-cm photons. So, the theory goes, if astronomers used a telescope to look at this 21-cm radiation in the millennia following recombination, first they would see a largely uniform signal from the neutral hydrogen, then later it would

appear riddled like Swiss cheese with “bubbles” of ionized gas surrounding early stars and galaxies. Eventually, these bubbles would merge and finally fill all of space with ionized gas. By mapping the history of reionization in this way, astronomers could refine their theories about what caused it. “Because of the complex astrophysics within galaxies, it’s not really predictable how the transition happened. The observations could surprise us,” says theorist Rennan Barkana of Tel Aviv University in Israel.

LOFAR and its kin won’t look for the 21-cm photons that hydrogen molecules emit; those signals are so weak they would be swamped by closer sources of radiation. Instead, astronomers will watch for signs that hydrogen is absorbing 21-cm radiation. To spot such “absorption lines,” they will need another source of radiation to act as a backlight. One possibility is the CMB, a small part of which has a wavelength of 21 cm; another is to use radio-loud quasars that formed early in the EOR to illuminate stages that came later. Because the universe is expanding, the redshift will have stretched the 21-cm radiation to a wavelength of 1.5 to

10 meters by the time the signal reaches Earth—exactly the range in which telescopes such as LOFAR are most sensitive.

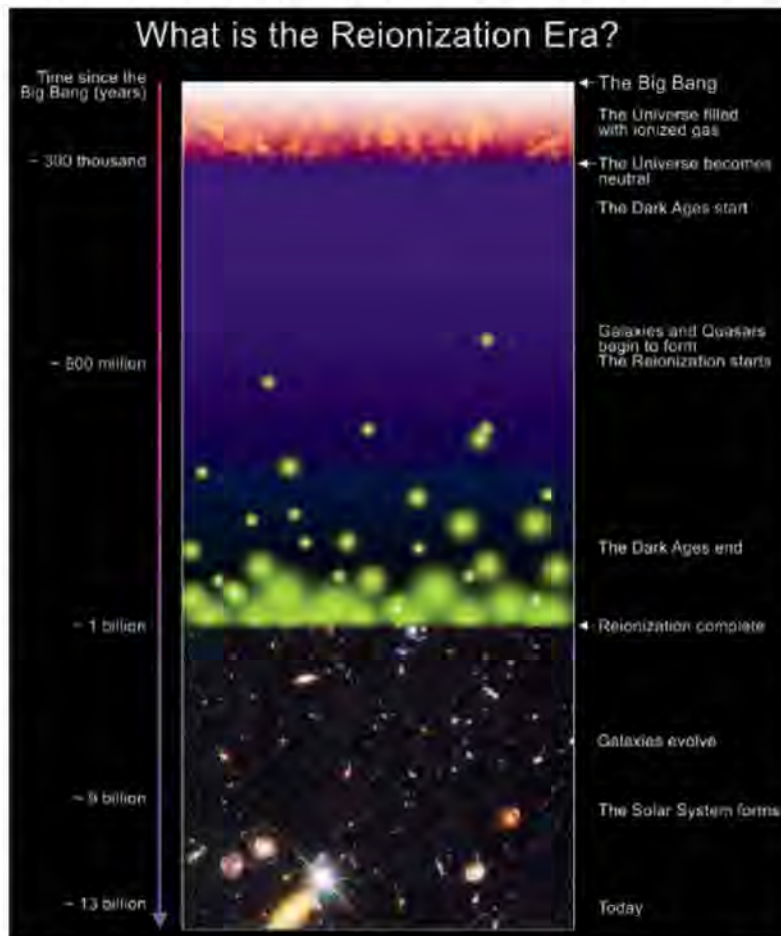
A new kind of telescope

The idea of trying to detect the 21-cm signal has been kicking around for decades, but astronomers had largely ignored this part of the spectrum because the long wavelengths would require huge dishes and would achieve poor results in angular resolution. Also, this frequency range is riddled with terrestrial noise, in particular the FM radio waveband, which is slap in the middle of it. But a number of theory papers in the 1990s and advances in digital signal processing encouraged astronomers to take a shot at it. In the late 1990s, astronomers at the ASTRON institute in Dwingeloo, the Netherlands, designing the Square Kilometer Array (SKA), a radio telescope to be built in Australia or South Africa starting in 2014, latched on to the idea of building a prototype scope for 21-cm radiation. They teamed up with several research groups in the United States to form the original LOFAR collaboration.

In 2003, the Dutch government offered the

ASTRON team €70 million to build the telescope in north-east Holland. Some of the U.S. partners had favored remote sites in New Mexico or Australia to avoid FM interference. But the ASTRON team reckoned that with clever design and signal processing, it would be possible to operate LOFAR in the noisy environment of the Netherlands. Their partners thought the risk too great, and the collaboration broke up. “It was affected by politics. What can you do?” asks Barkana.

ASTRON pushed ahead, testing antenna designs in the field, before beginning main construction this year. The plan is for ASTRON to build 36 antenna stations, each the size of a football field; 18 will form a compact core near the town of Emmen, and another 18 will be positioned across northern Holland. Each station sports 96 low-band (30–80 MHz) antennas, the squat flagpoles, and 48 high-band (120–240 MHz) antenna tiles, the low gray boxes, each containing 16 antennas. New international



Terra incognita. Astronomers and cosmologists have no data about the “dark ages,” when the first stars, galaxies, and large-scale structures formed. The new generation of long-wavelength radio telescopes will try to peer into the era of the first galaxies.

partners—Germany, the United Kingdom, France, Sweden, and perhaps others—will host additional stations to increase the baseline area of the telescope, improving its angular resolution. “It’s a plug-and-play system. If you have a fast connection and a field, you can join in,” says Rob Fender of the University of Southampton, head of the U.K. LOFAR team.

Getting the antennas in position, however, is the easy part. Managing the flood of data is when it gets hard. The full set of antenna stations, Fender says, will produce as much raw data as CERN’s Large Hadron Collider particle accelerator. LOFAR does not have the computing resources to archive that much data, so computers at each station will validate and process data on the fly, winnowing it down by more than 90%. The resulting data streams are sent via a fiber-optic network to the University of Groningen, where an IBM Blue Gene/P supercomputer correlates them and begins the complex task of subtracting various foreground signals, leaving data products that astronomers can study.

Garrett says six stations, including the first of five German stations, are complete and sending data. “Each few weeks more stations come online,” he says, adding that the telescope should be completed next year. The Groningen computer has constructed LOFAR’s first images, of bright radio sources at cosmological distances. “The data look fantastic. The quality is breathtaking,” Garrett says. Some frequencies are affected by interference, he says, but he’s confident that LOFAR’s digital processing can handle them. Conventional radio astronomy will start soon; collecting enough data to distinguish the faint EOR signal will take longer. “We will learn over years how [interference] will affect sensitive measurements like the EOR,” Garrett says.

Meanwhile, other telescopes are also gearing up to search for the 21-cm signal. LOFAR’s nearest rival may be the Murchison Widefield Array (MWA), a telescope being built in Western Australia. The project is led by some of the original LOFAR collaborators at the Massachusetts Institute of Technology’s Haystack Observatory, now teamed up with other researchers in the United States, Australia, and India. Colin Lonsdale, director of Haystack, says they have built a “late-stage

prototype” and plan to finish the array during 2010. LOFAR’s huge collecting area and high resolution make it a general-purpose, low-frequency observatory, Lonsdale says. MWA, by contrast, is optimized for the EOR. Although it has lower angular resolution, its wider field of view is better matched to collecting statistical information about reionization, Lonsdale says.

Another contender is the 21 Centimeter Array (21 CMA) in western China. Originally

ing under gravity, the size of bubbles of ionized gas around the first galaxies, and areas where early sources have heated up the intergalactic hydrogen. Such information, Lonsdale says, will help theorists to improve their theories of the history of the EOR. “It’ll take at least 3 years to accumulate data and understand it. We’ll get detection but not details,” says Meiksin.

Such results will likely just whet cosmologists’ appetite to delve deeper into the

EOR with bigger, more powerful telescopes. “If we detect the EOR, anything can happen,” says Garrett. One obvious candidate for a second-generation machine is the SKA, whose design—which is still in development—will include antennas designed for low frequencies. An EOR telescope of that size would take observations to a whole new level. It would be able to image the ionized bubbles as they formed around new galaxies. And by varying the

wavelength of the images, researchers can perform tomography, imaging slice after slice at different distances to build up a three-dimensional map of the ionizing universe. “With SKA we’ll really start answering questions,” Meiksin says.

And astronomers are already thinking about what might come after that. In a worst-case scenario, LOFAR and its kind “could illustrate that we can’t do this from the ground,” says Joseph Lazio of the Naval Research Laboratory in Washington, D.C. So several groups are starting to design telescopes for the far side of the moon. Such a project could make use of NASA’s upcoming Ares heavy-lift launcher to deliver a package of material to land robotically on the far side. An autonomous rover would then distribute antennas over a 10-kilometer area, leaving a central processing and communications center at the landing site. There, far from earthbound radio transmitters and the distorting effects of the ionosphere, astronomers could peer straight into the heart of the universe’s dark age. “It would allow us to see hydrogen before it became complicated by stars, galaxies, and quasars—a complex astrophysical brew—when the imprint of cosmological processes would be much easier to measure,” says Lonsdale. From such a vantage point, we would get a view of the universe before stars were born.

—DANIEL CLERY

IN SEARCH OF REIONIZATION

	Location	No. of antennas	Baseline	Completion
Low Frequency Array (LOFAR)	The Netherlands	44,160	1500 km	2010
Murchison Widefield Array (MWA)	Australia	8,192	3 km	2010
21 Centimeter Array (21CMA)	China	10,287	6 km	2006
Long Wavelength Array (LWA)	New Mexico, U.S.A	12,800	400 km	2010
Precision Array to Probe Epoch of Reionization (PAPER)	Australia	32		2009
Experiment to Detect the Global EOR Signature (EDGES)	Australia	1		2009–2012
PROPOSED				
Hydrogen Epoch of Reionization Array (HERA II)	Australia	5,000		2017
Square Kilometer Array (SKA)	Australia or S. Africa	50 million	3000 km	2018–2022
Lunar Radio Array (LRA)	Far side of the moon	~ 100,000	10 km	2020–2030

the brainchild of Jeffrey Peterson of Carnegie Mellon University in Pittsburgh, Pennsylvania, and Ue-Li Pen of the Canadian Institute for Theoretical Astrophysics in Toronto, the array began as a collaboration with Chinese researchers who eventually took over the project. The 21CMA was completed in 2006 and has been taking data, but Peterson says funding problems have made its observations sporadic.

Cosmological tomography

Although these first-generation low-frequency telescopes will be able to form images of closer radio-emitting objects, they probably won’t collect enough photons to image any features in the 21-cm signal. But their statistical measurements will still provide valuable information for cosmologists. The longer radiation spends traveling through space, the more the redshift lengthens its wavelength. So by looking at the 21-cm signal in different wavelengths, astronomers can effectively follow it forward and backward in time. Measuring the signal’s intensity at different wavelengths should enable them to track the disappearance of the universe’s neutral hydrogen during the EOR.

Researchers also hope to extract power spectra, measures of how the signal power varies over different angular scales. These spectra can reveal a number of things, such as the extent of clumps of hydrogen collaps-



Down to work. Seismologists are continually transplanting their subterranean seismometers to paint a seismic image of the deep Earth.

GEOPHYSICS

Scoping Out Unseen Forces Shaping North America

As it sweeps across America, the USArray network of seismometers is revealing an impressive but often befuddling subsurface menagerie of slabs, drips, and plumes

Unlike geologists, who can reach only a few kilometers below Earth's surface, geophysicists routinely probe thousands of kilometers down in search of the ultimate forces that created and still shape the ground we tread. But so far, geophysicists' picture of Earth's interior has been maddeningly fuzzy. To sharpen it, they are scanning the deep subsurface as never before, pushing a fly's-eye-like network of seismometers across the lower 48 U.S. states. Researchers "are jumping up and down" with all the new data, says seismologist Edward Garnero of Arizona State University (ASU), Tempe. "We're pretty ecstatic."

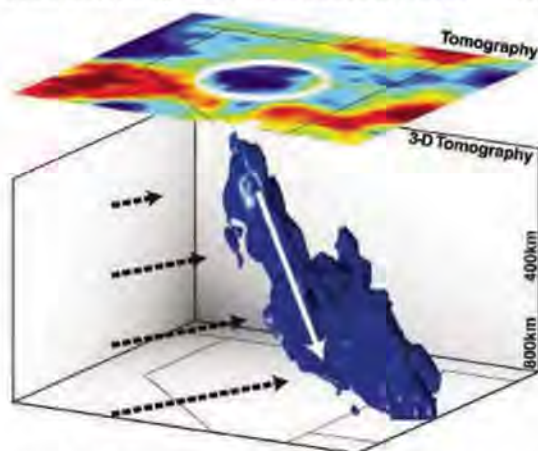
And sometimes they're pretty bewildered. "There are so many [imaged] structures under the western U.S.," says seismologist Eugene Humphreys of the University of Oregon, Eugene. It's like "we just wandered into a dark room and someone turned on the lights. We're struggling to make sense of it." Clearly, the great blobs and chunks of rock rising, sinking, or just floating beneath the surface bear some relation to overlying mountains, basins, and volcanic outpourings, but even the avalanche of new data can't always resolve exactly what the imaged features are or how they are shaping the surface.

A creeper-crawler camera

The data surge comes courtesy of the U.S. National Science Foundation's (NSF's) \$25-million-a-year EarthScope program,

now early in its second 5-year run. EarthScope's three-pronged approach is creating an evolving three-dimensional picture of the North American continent. In one component, researchers drilled through the San Andreas fault (*Science*, 12 October 2007, p. 183). In the second, they are gauging the changing strain on the crust as it is deformed by deep stirrings and jostling tectonic plates.

EarthScope's third component—the \$13.6-million-a-year USArray program—looks much deeper. The USArray system records seismic waves from distant earthquakes after they've passed through—and been altered by—the rock beneath North



What a drip! Seismic waves that are slower or faster than normal (blues or reds, top) can create a 3D image (blue, bottom) of a sinking "drip" tilted by "blowing" mantle rock (dashed arrows).

America. USArray involves three kinds of seismic networks: a Reference Network of 100 seismometers permanently installed 300 kilometers apart in a loose grid across the lower 48 states; a Flexible Array of 446 seismometers that are typically placed 10 kilometers or so apart for a few months or years to study a feature of particular interest; and the novel Transportable Array, an 800-kilometer-wide net of 400 advanced seismometers 70 kilometers apart.

The novelty of the Transportable Array is its combination of broad coverage, relatively dense instrument spacing, and mobility. The array started out hard against the West Coast in 2004 and has been steadily creeping eastward. Today its net spreads 2000 kilometers along the Rocky Mountains from the Canadian border to the Mexican border. Each month, about 18 instruments on the west side of the array that have collected a couple of years' worth of data are removed from their 2-meter-deep vaults and reinstalled on the east side. Reusing the equipment keeps the project affordable. Over the course of 10 or 12 years, the Transportable Array will occupy 1600 locations from coast to coast. Since 2004, all of USArray has generated 14.3 terabytes of data, nearly as much as the Global Seismographic Network has produced since 1988.

The more data collected and the more closely spaced the instruments, the sharper the pictures of the interior. The most heavily used seismic imaging technique—seismic tomography—works like a computed tomography (CT) scan of the human body. In a CT scan, different body parts absorb x-rays to different extents; in seismic tomography, it is rock's varying effect on the velocity of seismic waves that paints the picture.

Waves pass through colder rock faster, for example—yielding a patch of blue in tomographic images—and through hotter rock more slowly, rendered as red.

A deep zoo

For the first time, seismic tomographers are incorporating substantial amounts of USArray data into images of the deep western United States. Already, the new images have added fuel to a long-running debate over the existence of mantle plumes (*Science*, 22 September 2006, p. 1726). One contingent of researchers studying tomographic images had seen these

CREDITS (TOP TO BOTTOM): COURTESY OF THE INS CONSORTIUM; FIGURE ELEMENTS FROM J. D. WEST ET AL., NATURE GEOSCIENCE 2, 439-444 (24 MAY 2009), REPRINTED BY PERMISSION FROM MACMILLAN PUBLISHERS LTD.

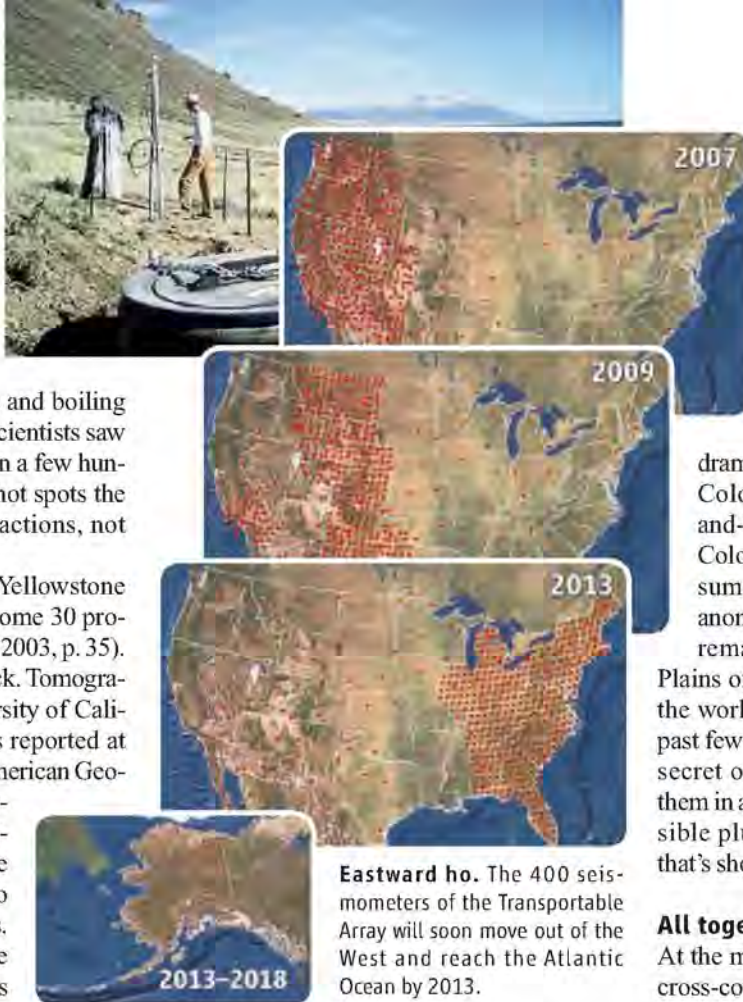
tall columns of hot rock rising thousands of kilometers from deep in the lower mantle like smoke from a stack. Where plumes reach the surface, those researchers say, the rising hot rock melts and feeds hot spots like the volcanoes of Hawaii or Iceland or the geysers and boiling pools of Yellowstone. But other scientists saw hot rock extending no deeper than a few hundred kilometers and considered hot spots the products of tectonic plate interactions, not heat from the deep interior.

The putative plume beneath Yellowstone was among the most suspect of some 30 proposed plumes (*Science*, 3 January 2003, p. 35). But with USArray it's coming back. Tomographer Richard Allen of the University of California, Berkeley, and colleagues reported at last December's meeting of the American Geophysical Union (AGU) that Transportable Array data add to evidence of a seismically slow zone beneath Yellowstone extending to a depth of at least 1000 kilometers.

"The whole history of mantle plumes makes you hesitate," says Allen. Still, he says, "I feel pretty confident about a plume to lower mantle depths." Unlike the bolt-upright columns geoscientists imagined when they first conceived of plumes in the 1970s, Allen says, his group's Yellowstone plume slants to the northwest through the upper mantle and balloons into a much broader slow zone below 660 kilometers in the lower mantle. It even seems to have torn the cold slab of oceanic plate sinking eastward through the upper mantle under the continent.

Other researchers, however, see different pictures. Seismologist Matthew Fouch of ASU Tempe agrees that there's "no clear evidence of a simple mantle plume" beneath Yellowstone. Rather than a contorted columnar plume, Fouch and colleagues say, their processed seismic data show a bent, thin "hot sheet" extending between shallow and deep blobs of hot rock. But when seismologist Rob van der Hilst of the Massachusetts Institute of Technology in Cambridge looks at his and others' tomographic images, he finds that "it's hard to say if [the hot feature] is continuous." Whether there's a single tall plume or a random series of unconnected blobs "is still up in the air," he says.

Some other creatures in the tomographic zoo are proving easier to interpret. Recognized decades ago, the Isabella Anomaly is a blob of rock lying 70 kilometers to 250 kilometers beneath the western edge of the Sierra Nevada mountains of central California. Seis-



Eastward ho. The 400 seismometers of the Transportable Array will soon move out of the West and reach the Atlantic Ocean by 2013.

mic waves pass through it unusually fast, prompting speculation that it is denser due to the composition of its rock. That higher density might have made it fall away (or drip away, as geophysicists say) from the base of the Sierra Nevada. Relieved of that burden, the less dense crust could have floated up to form high mountains.

In part to test the Sierra Nevada drip idea, seismologists led by George Zandt of the University of Arizona, Tucson, superimposed the Flexible Array on the Transportable Array as it was passing over the Isabella Anomaly. The sharpened view showed a narrower anomaly than before, which allowed the group to calculate a density for the anomaly's rock. It turns out to be so dense that it must contain just the kind of rock hypothesized to have dripped away from the base of the Sierra Nevada, Zandt, William Levandowski of the University of Colorado (CU), Boulder, and the rest of the group reported at the AGU meeting. The group concludes that the drip could have triggered the Sierra Nevada's uplift.

Other seismic anomalies both fast and slow are now getting close looks in USArray data. In the June issue of *Nature Geoscience*, seismologist John West of ASU Tempe, Fouch, and colleagues reported that they had discovered a 500-kilometer-tall drip beneath south-central Nevada, tilted to the northeast by slowly flowing mantle rock "blowing" in that direction.

The flow of the Great Basin Drip tugging on the crust would explain a mysterious patch of crust under compression amid the Great Basin's pervasive crustal extension, the group says, although others see mantle flowing around a slab fragment rather than a drip.

The Aspen Anomaly, a stretch of rock that slows seismic waves dramatically, sits directly beneath 80% of Colorado's 14,000-foot-(5100-meter)-and-higher peaks as well as the ore-rich Colorado Mineral Belt. Researchers presume there's a connection between the anomaly and the mineralized uplift, but it remains unproven. And the High Lava Plains of southeastern and central Oregon—the world's largest volcanic province of the past few million years—must be guarding the secret of their origins somewhere beneath them in a mix of sinking slab fragments, a possible plume tail, and flowing mantle rock that's showing up in the latest data.

All together now

At the midpoint of the Transportable Array's cross-country march, researchers wish USArray were yielding more insights and prompting less squabbling. "We're getting a clearer vision in the West," says van der Hilst, but "when you look at the details, people do see different things. The [tomographic] models allow for different interpretations." Fouch notes that with each group's different processing of the same data, "you can let tomography become a Rorschach test."

Researchers say they'll soon find better ways to interpret USArray observations. "It's such an unwieldy mass of data," says geophysicist Craig Jones of CU Boulder. "Playing with it is a different game than we're used to. I have a feeling we'll be seeing in the next 5 years analyses far more imaginative than what we've done so far." Some innovative new techniques are already on the horizon. For one, seismologists are starting to use background seismic noise generated by ocean waves—so-called ambient noise—to form tomographic images.

And then there are the geologists. EarthScope was originally supposed to bring geophysicists and geologists together (*Science*, 26 November 1999, p. 1655). Funding shortfalls early in EarthScope frustrated the marriage, but now NSF is managing to fund more geological work in and out of EarthScope. Relating geological traces at the surface to underlying seismic anomalies could help explain why there's such a weird assortment of still-active deep processes shaping the surface of the American West. —RICHARD A. KERR



LETTERS

edited by Jennifer Sills

Preserving Starry Nights

THE 24 APRIL NEWS FOCUS STORY "STARS IN DUSTY FILING CABINETS" (Y. BHATTACHARJEE, p. 460) describes well the need to preserve astronomical glass plate collections and the difficulties encountered in doing so. The Carnegie Institution has a collection of some 200,000 plates of all kinds, gathered over decades from Mount Wilson Observatory, Palomar, and Las Campanas Observatory. Private funding has allowed us to preserve and archive the direct astronomical image and spectrographic plates in the collection, and small sets of these plates have been digitized when researchers needed them. Similarly, a project headed by Roger Ulrich at the University of California at Los Angeles and funded by the National Science Foundation has digitized large sections of our solar plates; these scans can be seen at www.astro.ucla.edu/~ulrich/MW_SPADP/index.html. In total, 39,500 plates (including direct image,

spectra, and solar plates) have been digitized so far.

As the news story notes, space and funding needs for current projects often take away from efforts to preserve old data. Hopefully, greater awareness of the value of such plates, which are our only record of the past night sky, will lead to a corresponding increase in support for their protection.

WENDY FREEDMAN

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Forecast for Reproducible Data: Partly Cloudy

M. R. NELSON'S PERSPECTIVE "BUILDING AN Open Cloud" (26 June, p. 1656) projects a vision of scientific computing that is enticing in some ways, but worrisome in others. Scientists can benefit considerably from being able to tap vast computing resources without knowing where the data or processing software reside or how these resources are provided. But ignorance of the nature—and more important, the provenance—of such resources creates novel problems for science and scientists.

Repeatability, reproducibility, and transparency are the hallmarks of the scientific enterprise. As more and more scientific research in every field is based on elaborate computation (1), it becomes more and more challenging to reproduce the results of these computations (2). This challenge is greatest when computational resources are propri-

etary and unknown even to the scientists who use them, as is the case for Nelson's "Many Clouds" and "Hazy Skies" scenarios. These two scenarios raise the specter that even the scientists producing and publishing results from Cloud computation will be unable to reliably reproduce their results, thereby undermining one of the foundations of scientific research.

The importance of documenting the provenance of scientific data—including the algorithms, tools, and versions of software used to generate it—is increasingly understood by scientists from a wide range of disciplines to be a problem of fundamental importance (3, 4). Computing in the Cloud will complicate this problem, which—although by no means insoluble (5, 6)—should be added to Nelson's list and viewed as a counterweight to the advantages of putting enormous amounts of anonymous computational resources at the ready disposal of scientists.

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Response

OSTERWEIL *ET AL.* ARE RIGHT TO HIGHLIGHT how it will become increasingly difficult for the work of one research team to be precisely reproduced by another as the size and complexity of computational research problems grow. Very subtle differences in computer hardware, operating systems, math libraries, and applications software can be compounded when trillions of calculations are done and petabytes of data are stored and transferred.

Cloud computing will make this problem even more important and provide even more incentive to address it properly. The good news is that the Cloud, by providing easier and cheaper access to computing cycles and storage, will make it far simpler to detect the very subtle hardware and software problems that can lead the same applications software to yield different results for the same inputs (1, 2). Because Cloud computing can dramatically cut the cost of computing, researchers will be able to run their problems multiple times on different platforms. Furthermore, they will more easily be able to do the thorough testing required to spot discrepancies, and to design software that is less susceptible to subtle variations in the implementation of particular algorithms.

Computer scientists and mathematicians should be able not only to help the computational research community, but also to develop techniques that can be used in the full range of commercial Cloud computing applications. As Osterweil *et al.* stress, there are ways to tackle the reproducibility problem,

but more research is needed to avoid delaying the adoption of Cloud computing for research and commercial use. Even with technical solutions, legislation and regulation may need to be modified to account for the fact that companies rely more and more on a computing infrastructure that is constantly in flux.

As Osterweil *et al.* note, technical solutions will be far easier to implement if the evolving Cloud is built on open standards and nonproprietary code—the “Blue Skies” scenario I described. This will make it far easier for computational scientists to build the tools that enable them to monitor precisely how their algorithms are being run and how their data is being stored and analyzed, no matter where in the Cloud that happens.

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Immune System: Not So Superior

IN HIS NEWS FOCUS STORY “ON THE ORIGIN of the immune system” (1 May, p. 580), J. Travis nicely lays out some of the issues surrounding the evolution of the adaptive immune system, particularly the biologically novel VDJ recombination process. The selective advantage of the adaptive immune system is, however, not at all clear. Citing the view of “many immunologists,” Travis describes the notion that the adaptive immune system allowed more complex organisms to deal with

more complex threats. He also cites Craig Thompson’s suggestion that the adaptive immune system conserves resources, implying that the innate immune system is more resource intensive. These arguments fail by simple inspection. Whatever organismal complexity means, there is no evidence that invertebrates are less complex than gnathosomes or agnatha (which has its own version of adaptive immunity). On the issue of resource intensity, as T. Pradeu points out in his reply (“Immune system: ‘Big Bang’ in question,” Letters, 24 July, p. 393), the adaptive immune system never works on its own; it is activated first by an intensive innate response. In addition, adaptive immunity further amplifies innate reactions. An equally likely possibility is thus the adaptive immune response, with its high rate of cellular expansion and contraction, is actually more resource intensive. In any event, neither of these conjectures has been supported by experimentation.

The underlying theme of the Travis news story as well as the reply by A. M. Silverstein (“Immune system: Promethean evolution,” Letters, 24 July, p. 393) is that the adaptive immune system is somehow a great advance (“Big Bang”) in the evolution of free-living organisms. Proponents of this view would thus be obliged to show that gnathosomes have a

LIFE IN SCIENCE

Having a Blast in Kenya

Our task? To position and detonate two 1000-kilo explosive charges on the bottom of Kenya’s Lake Turkana. The year was 1990, and these blasts would allow seismometers placed up and down remote parts of the East African Rift to record sound waves from explosions and measure the structure of crust being pulled apart. To collect accurate data, we had to detonate the explosions exactly on time. As an inexperienced graduate student, my job was to pilot the Zodiac raft laden with plastic explosives. Setting the charges on the glassy lake in the morning was easy; we just had to pitch the explosive sausages overboard into a big pile on the lake bottom. We cleverly marked the shot locations with buoys made from empty water jugs anchored with rocks.

Returning in the afternoon, we found that the wind had stirred up the lake surface into considerable swells. Finding the small white buoys in a sea of whitecaps was challenging. We found the first of the two, attached the electrical line, reeled off 500 feet

of cable, and detonated without incident. But now we had only 10 minutes to find the second, and the wind was fierce. After 9 minutes, we located the small jug. We had time to back off only about 100 feet before hitting the button. The result? Nothing.

What we didn’t know was that the



wind had blown the buoy about 100 feet away from the charge, dragging its inadequate anchor with it. That shift placed us directly above the explosives. So, although we didn’t see the plume of water come off the shot, it wasn’t long before we felt it. The blast launched the Zodiac and crew into the air. I dangled from the outboard motor and landed back in the lake with the raft, but my two companions were flung into the water. Luckily, the blast had scared the crocodiles away.

Under a rain of dead tilapia and muddy water, we hauled back into the boat and started it up. Our only wounds were bruised bottoms from the force of the blast under us. We limped back to shore, where a Kenyan Ministry official had come to keep tabs on us and our effects on the fish. We approached him sheepishly, but he only commented that the second blast had seemed much smaller than the first.

TOM PARSONS

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EDITOR’S NOTE

This is an occasional feature highlighting some of the day-to-day humorous realities that face our readers. Can you top this? Submit your best stories at www.submit2science.org.

reduced incidence of mortality associated with disease, but I know of no such evidence. In fact, invertebrates are plagued by many of the same families of viruses, bacteria, and protists as vertebrates, and yet they do not exhibit high mortality rates due to infection nor do their populations collapse under the weight of parasitism. In fact, the immune system may be the cause of its own necessity (1). Incremental immune evolution surely confers a selective advantage, but such an advantage is quickly countered by the more facile evolution of thousands of parasitic agents. Over eons, there has grown an immune appendage that is nonetheless unable to decrease the overall burden of parasitism. This principle was described by van Valen as "The Red Queen Hypothesis" (2).

The notion that the immune system plays the bouncer, raising the velvet rope for beneficial bacteria and giving attitude to their less desirable brethren, was taken one step further by Margaret McFall-Ngai. She proposed that the adaptive immune system evolved, in part, to recognize and manage complex communities of beneficial microbes living on or in vertebrates (3). In summary, comparative genomics has shown various components of the immune sys-

tem to be under continuous positive selection, and yet we cannot assume we know the basis for this selective pressure (4). STEPHEN M. HEDRICK

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Infants' Perseverative Search Errors Are Induced by Pragmatic Misinterpretation"

John P. Spencer, Evelina Dineva, Linda B. Smith

Topál et al. (Reports, 26 September 2008, p. 1831) proposed that infants' perseverative search errors can be explained by ostensive cues from the experimenter. We use the dynamic field theory to test the proposal that infants encode locations more weakly when social cues are present. Quantitative simulations show that this account explains infants' performance without recourse to the theory of natural pedagogy.

Full text at www.sciencemag.org/cgi/content/full/325/5948/1624-a

RESPONSE TO COMMENT ON "Infants' Perseverative Search Errors Are Induced by Pragmatic Misinterpretation"

József Topál, Mária Tóth, György Gergely, Gergely Csibra

Spencer et al. argue that infants' perseverative search errors cannot be ascribed to an interpretive bias induced by communicative cues as we proposed. We argue that their model leads to different predictions about infant behavior from those derived from natural pedagogy in certain situations and therefore fails to provide a viable alternative to ours.

Full text at www.sciencemag.org/cgi/content/full/325/5948/1624-b

Letters to the Editor

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PATENT LAW

One Size Fits All, After Tailoring

Rebecca S. Eisenberg

In *The Patent Crisis and How the Courts Can Solve It*, Dan Burk and Mark Lemley synthesize their own and others' prior work to advance a provocative claim about the U.S. patent system: It is not a unitary, one-size-fits-all regime, applying the same rules across all fields of technology. Rather, it is a flexible system with numerous "policy levers" that courts manipulate to adapt general rules to meet the needs of different industries. This judicial flexibility is a good thing, the authors maintain, because it allows the patent system to adapt to varied and changing needs across the increasingly diverse spectrum of innovation.

Burk and Lemley (law professors at, respectively, the University of California, Irvine, and Stanford) cite considerable scholarly evidence that patents play different roles in different industries. For example, survey responses reveal that patents provide valuable incentives for innovation in the pharmaceutical industry, while they serve primarily as a defensive shield against the patents of competitors in the semiconductor industry. The authors observe a similar diversity in theories of patent law, noting that different theoretical models track the divergent experiences of different industries. In recent years, these differences across industries have prompted divergent responses to patent reform proposals, thus leading to legislative stalemate. In other words, one size manifestly does not fit all, either in theory or in practice.

Meanwhile, Burk and Lemley note, the courts have achieved some of the goals of patent reformers without awaiting new legislation. Judicial manipulation of policy levers is preferable, they argue, to legislative fine-tuning of the statute for a number of reasons: Congress is bound by treaty to maintain a nominally unitary patent system. It is slow to adapt to shifting technological and economic conditions. It is too responsive to special-interest lobbying to be trusted to enact socially desirable rules. Nor do the authors trust the Patent and Trademark Office, with its vulnerability to "capture" by the patent-seekers it serves, to

make the necessary adjustments. Instead the authors would look to the courts to tailor the broad rules of patent law laid down by Congress on a case-by-case basis.

They highlight a number of policy levers that the courts have deployed—sometimes "accidentally or implicitly" rather than expressly—to apply patent law "with sensitivity to the characteristics of particular industries." For example, the statutory requirement of "nonobviousness" calls for an evaluation of an invention from the perspective of a "person having ordinary skill in the art," an approach that effectively sets a higher threshold in fields with higher skill levels. Even without such an explicit invitation, Burk and Lemley observe, the courts discriminate by field in their application of statutory standards. For instance, they allow applicants for software patents to get away with a broad disclosure of the function of the software, without having to disclose code, whereas applicants for gene patents must disclose not only the gene's function but also its complete DNA sequence. As a result, patent applicants are able to claim inventions more broadly in the software field than in the genetics field.

These and other examples of "policy levers" that Burk and Lemley would have the courts use to fine-tune the system generally track differences across fields of technology. However, the theoretical models that they turn to for guidance track economic factors that differ across industries. Sometimes the two go hand in hand, but not always: The authors note, as an example, that the automobile industry files many patents on software. Although the authors sometimes observe this distinction, sometimes they ignore it—making their thesis and its implications less crisp.

Discrimination based on field of technology is inherent in a legal regime that evaluates patents from the perspective of practitioners in the field, and such discrimination finds considerable authority in the text of the Patent Act. The Patent and Trademark Office and the courts

have ready access to the technological information necessary to make these judgments and considerable experience in applying the standards. Discrimination based on industry would seem to call for a qualitatively different inquiry into the economic impact of patents in different industries, an inquiry for which there is little statutory authority or legislative guidance. In some cases, the authors applaud the courts for making appropriate distinctions accidentally or implicitly. In others, they criticize them for doing the opposite of what sound economic analysis would recommend. This suggests that courts may need better economic information to work the levers right.

Perhaps expert testimony from economists could guide the courts toward more efficient deployment of policy levers, but explicit case-by-case consideration of economic impact on a particular industry would represent a significant departure from current practice. Even sympathetic judges might be skeptical about their authority to consider such economic information and puzzled about how to use it. Judges would likely deny that they currently discriminate by field or by industry in the application of patent law. If persuaded that they have indeed been discriminating, they might be more likely to correct themselves in the future than to make the discrimination explicit (and better informed).

The Patent Crisis and How the Courts Can Solve It

by Dan L. Burk and Mark A. Lemley

University of Chicago Press, Chicago, 2009. 228 pp. \$45, £31. ISBN 9780226080611.



First U.S. patent. On 31 July 1790, Samuel Hopkins was granted a patent for his "new apparatus and process" in the making of pearl ash and pot ash.

Although the book's title implies that Burk and Lemley see the courts as their audience, this is hardly a how-to book for courts. The authors recognize that much more work needs to be done to figure out how best to take account of industry differences in the implementation of patent law. Their argument is embedded more in scholarly discourse than in judicial opinions, and readers not already participants in that discourse will not find this compact book an easy read. Those who persevere will be rewarded with a fascinating introduction to a scholarly literature that, at least so far, raises as many questions as it answers.

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MOLECULAR BIOLOGY

Doing Magic with DNA

Alfonso Mondragón

The structure of DNA has been one of the most influential findings in science. In the structure, the two antiparallel strands are intertwined. This can lead to some serious problems, which Watson and Crick noted in a paper (1) they published a month after their description of the model of the DNA double helix. They wrote "Since the two chains in our model are intertwined, it is essential for them to untwist if they are to separate. ... Although it is difficult at the moment to see how these processes occur without everything getting tangled, we do not feel that this objection will be insuperable." Indeed, the objection was not insuperable. Nonetheless, it took years before there was an answer to the entanglement problem. In 1971, James Wang discovered the first type I topoisomerase (2). The next year, James Champoux and Renato Dulbecco identified mammalian topoisomerase I (3). Then in 1976 Martin Gellert, Kiyoshi Mizuuchi, Mary O'Dea, and Howard Nash found the first type II enzyme, bacterial gyrase (4). With these findings, what once looked like a formidable obstacle to understanding many biological problems disappeared or at least receded. Now we know that topoisomerases are everywhere, solving many topological problems associated with the double-helical nature of DNA. But like any good essential supporting actor, they play their role and make things possible without taking the limelight away from the central players.

In *Untangling the Double Helix*, Wang offers a very accessible and thorough introduction to DNA topoisomerases, from their basic properties to their roles in biology and medicine. The author's important contributions to the development of the field allow him to provide a lively account of the discovery and subsequent characteriza-

tion of this family of enzymes. The book is enjoyable and easy to follow, with clear illustrations to help explain several major points.

In the early chapters, Wang gives a frequently personal account of the experiments, observations, and apparent contradictions behind the search for a solution to the entanglement problems associated with DNA. Now that we know so much about topoisomerases, people sometimes forget that at one point the topological problems that these enzymes solved appeared not to have an explanation. These opening chapters also provide clear descriptions of the different types of topoisomerases, their structures and biochemical characteristics, and the different mechanisms used by them. Wang lucidly answers the question of how topoisomerases work. In addition, he explains methods used to study topoisomerases, including recent experiments using single-molecule techniques.

The later chapters address related questions: In which biological processes do topoisomerases play a role? And why do we need

Untangling the Double Helix
DNA Entanglement and
the Action of the DNA
Topoisomerases

by James C. Wang

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ISBN 9780879698638. Paper, \$45.
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them? Topoisomerases are involved in many cellular processes, including gene expression, replication, and recombination. They are essential players that solve very specific problems and allow these processes to occur. The author clearly and concisely touches on each

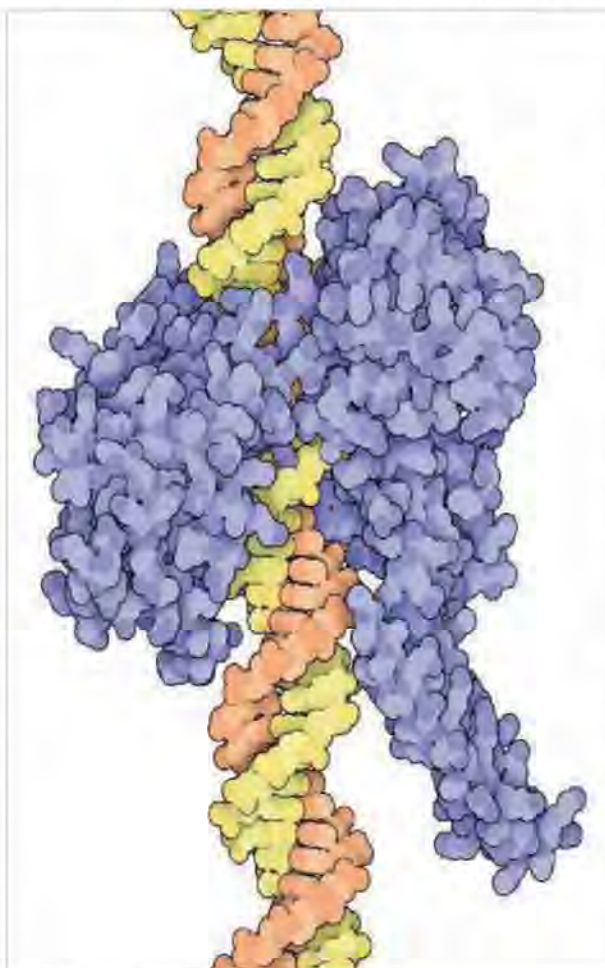
process and the topological problems associated with it, and he describes the way topoisomerases help facilitate it. Due to the oversimplified and reductionist view sometimes used to explain many cellular processes, it is easy to forget that many cellular transactions involving DNA work in concert with DNA topoisomerases. Wang succeeds in bringing topoisomerases back to center stage and reminding us that life as we know it would be impossible without them.

The crucial role of topoisomerases is emphasized in the last chapter, where Wang surveys their involvement in medicine. Many people may not be aware that some popular and widely used antibiotics and cancer drugs target topoisomerases. Readers will find that the chapter gives an excellent overview of topoisomerase-drug action, focusing on the ways drugs interfere with these enzymes.

Untangling the Double Helix offers an excellent introduction to DNA topoisomerases. The book is not, and does not try to be, a comprehensive and complete review of all aspects of the field. Rather, Wang provides an easy-to-follow and sometimes personal account that touches on many aspects. (Many of the examples and references come from his own work.) His coherent overview will help readers understand the mechanisms and cellular roles of these enzymes. The book successfully aims at a general audience not necessarily familiar with topoisomerases or their biology. Anyone wishing to learn more about these enzymes or some of the ideas behind their discovery will find Wang's account illuminating. It makes a perfect companion to textbooks in biochemistry or molecular biology, demonstrating the advantage of presenting not only the facts but also the always interesting backgrounds to important discoveries.

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Human topoisomerase I.

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SCIENCE EDUCATION

Revising the AP Biology Curriculum

William B. Wood^{1,2}

At its Advanced Placement (AP) Program annual conference held in July, the College Board released a draft of its new curriculum for the AP biology course (1). Now used in thousands of secondary schools across the country, this course provides some of the best biology instruction in the United States to about 150,000 students every year. Given the growing interest in standards-based education and the absence of official U.S. national standards, AP courses have become increasingly important as *de facto* standards for high school students, particularly in the sciences. Therefore, it is essential that these courses conform to high standards of both content and pedagogy. As scientific and pedagogical knowledge have advanced in recent years, aspects of the AP program have come under criticism from educators, and revisions of the AP biology course in particular are overdue. The new AP biology curriculum represents a major step toward addressing this criticism. However, questions about its implementation still remain.

AP biology was developed in the 1950s as part of the AP program to offer college-level courses for advanced students in high schools. A major goal has always been to provide credits that students could use to place out of introductory college courses and thereby shorten the time to a degree. As the basis for awarding credit and advanced placement to incoming freshmen, colleges use performance on a single high-stakes test, the national AP examination, administered by the College Board through the Educational Testing Service. Because the AP exam is designed to test knowledge of topics taught in college introductory biology courses, in which most high school teachers received their first exposure to college biology, the content and, to a large extent, the pedagogy of these college courses have driven the design of previous AP biology curricula.

In 1999, the National Research Council (NRC) of the U.S. National Academy of Sciences convened a panel of scientists, educators, and high school teachers to review AP programs in science, assisted by content sub-

panels focusing on mathematics, physics, chemistry, and biology. The 2002 reports of the NRC panel (2) and the Content Panel for Biology (3) (referred to below collectively as the NRC panels) were critical of the AP biology program. During the same period, the College Board conducted its own internal review of AP biology (4), coming to some of the same conclusions as the NRC panels. This Education Forum discusses the NRC panels' major concerns and how the new AP biology course addresses them.

The Mile-Wide, Inch-Deep Problem

For the past few decades, biology has been growing explosively, in both knowledge about living systems and the number of students enrolling in college biology classes. Instructors and textbook authors have reacted by trying to cram more and more information into introductory college courses, which are generally taught to large classes, through traditional lectures that attempt to cover a broad array of subject matter. The AP biology exam of a decade ago tested primarily recall of factual information on a similar range of topics, and the AP biology curriculum emphasized factual learning rather than in-depth understanding of fundamental concepts. This emphasis was a consequence of an unrealistic goal, that students who achieved high scores on the AP biology exam should be able to place out of any introductory college course in the country, regardless of whether the course's primary focus was on molecular and cell biology or ecological, organismic, or evolutionary biology. The resulting AP curriculum was "a mile wide and an inch deep," putting pressure on teachers to cover all possible introductory college course topics and making a superficial approach almost unavoidable.

The emphasis on assimilating a large body of factual knowledge also encouraged traditional pedagogy (e.g., lectures and "cook-book" lab exercises) in AP biology, ignoring recent advances in cognitive science and educational research that have defined more effective approaches for student learning (5, 6). Again, this reflected the introductory

Major, welcome changes to the AP biology curriculum raise questions about implementation and assessment.

college courses that served as models for design and teaching of the AP course.

The NRC panels recommended changes in the AP curriculum and, more important, in the AP exam. AP biology should indeed be a college-level course, demonstrating the ability of AP students to do college-level work eligible for college credit. But courses should place less emphasis on comprehensive coverage and memorization of factual detail, and more on understanding of fundamental concepts, the process of science, and interdisciplinary connections, through more student-centered activities such as problem solving, inquiry-based laboratories, and active learning in the classroom.

What's New?

In the years since 2002, the College Board has introduced changes that began to address some of the NRC panels' concerns (7). The revised AP biology curriculum unveiled this summer, however, represents a new departure, substantially different from its counterpart of a decade ago in terms of both content and pedagogy. It encourages teaching prac-

THE FOUR "BIG IDEAS" OF THE NEW AP BIOLOGY CURRICULUM

- 1 Evolution as the basis for both the diversity and the unity of life
- 2 Biological systems and their properties, including energy use, molecular components, growth, reproduction, and homeostasis
- 3 Information: how organisms store it, retrieve and use it, transmit, and respond to it
- 4 Interaction of systems components and the emergent properties of the resulting entities, from DNA molecules to cells to organisms to ecosystems

tices that recent educational research has found effective (6) and promises to solve many of the problems described above.

The new curriculum is built on only four "big ideas," which apply to all areas of biology (see graphic above). It is noteworthy that evolution is in the foreground as the major organizing principle of biological science, given current controversy about its teaching. Under each of the four ideas, the curriculum defines "enduring understandings" (i.e., the major concepts), and specific learning objectives (i.e., what students should be able to do at the end of an AP biology course). Included in the learning objectives and emphasized throughout the curriculum are seven "science practices" that

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²The author was Chair of the NRC Biology Subpanel and editor of its report (mentioned below). He served from 2004 to 2005 on the College Board's AP Biology/NSF Advisory Committee and in 2008 on the AP Biology Redesign Review Panel.

students should learn to apply (see graphic below). Finally, to highlight the de-emphasis on memorizing facts, the curriculum specifically excludes some details (e.g., the structures of Krebs cycle intermediates) as being beyond the scope of the course and the AP exam.

Although it is not spelled out in the supporting material released so far, the new curriculum implies that AP teachers can, at least to some extent, pick and choose the specific topics they focus on in teaching the principles outlined above, so that different AP biology courses may differ in content. This implication and other questions about the new curriculum are discussed further below.

The development process for the new curriculum has dealt with concerns of the NRC panels about updating the AP course to better reflect the current state of biological sciences. Over the past 7 years, the College Board has enlisted several teams of educators and leading university scientists from all areas of biology to help redesign and rewrite the curriculum and supporting materials. Also under development are new inquiry-based laboratory projects that will give students opportunities to apply the seven science practices listed in the graphic below.

SEVEN SCIENCE PRACTICES THAT AP BIOLOGY STUDENTS SHOULD BE ABLE TO APPLY

- 1 Use models and representations
- 2 Use quantitative reasoning
- 3 Pose hypotheses to guide discussion and investigations
- 4 Plan experiments and data collection strategies
- 5 Perform data analysis and evaluate evidence
- 6 Work with scientific explanations and theories
- 7 Integrate and transfer knowledge across scales, concepts, domains, and disciplines

The Problem of Quality Control

The NRC panels also raised concerns about the lack of uniform standards for AP biology courses. With no required process for certification of AP teachers and school facilities, the quality of AP biology courses varied markedly between school districts across the country. The College Board has addressed this issue by instituting an AP course audit, in which all AP teachers from a given school must participate in order to receive authorization to use the "AP" label and have their courses listed in the AP course ledger made available to colleges and universities each fall. The College Board has also instituted new professional development workshops for AP teachers, which will have to be adapted to the new curriculum.

Preparation for AP Biology

Another concern of the NRC panels was that in some schools, students were allowed to take AP biology as their first, and sometimes only, science course. This practice necessitated watering down the AP course, contributing to the quality-control problem discussed above and preventing some students from reaching the level of learning required to perform well on the AP biology exam. To help remedy this situation, the College Board will not only urge schools to require a previous biology course as a prerequisite for AP biology, but will also set standards for such courses. These Science College Board Standards for College Success (8, 9) outline specific performance expectations, such as students' ability to apply the seven science practices. Widespread adoption of these guidelines could provide a valuable set of national performance standards for middle- and high-school science students.

Questions and Challenges

The College Board plans to release a few new inquiry-based labs annually, beginning this year, so that schools can transition gradually to the new curriculum. In December, the board will announce when the new AP biology course and exam will become required for all participants, probably in 2012 or 2013, but schools can start using the new curriculum as soon as they are ready.

Although the new curriculum is exciting and encouraging, it also raises questions about other aspects of the new program that are not yet released. The nature of the new AP exam, in particular, will be key to the program's success. How much will it shift the emphasis from recall to application of concepts? Will students be asked simply to memorize concepts as factual information or to apply them to new situations? How the exam is written will determine how concepts are taught. The learning objectives released so far are encouraging in this regard. They stipulate that students should achieve higher Bloom's levels of understanding [see figure 1 in (6)]: that is, be able to apply, compute, solve, predict, compare, create, design, evaluate, and criticize, rather than simply to define, name, describe, and explain. Also encouraging is that students will be allowed to use calculators on the new exam, permitting inclusion of questions that involve quantitative analysis using equations, graphs, and tables of data.

Will success on the exam still require knowledge of most topics in the curriculum, or will it include alternative questions targeting different areas from which students can choose? The answer to this question will dictate whether the course must still attempt to be comprehensive, or whether AP teachers will be able to follow a path through the new curriculum that best suits their interests and expertise without handicapping their students on the exam.

Finally, teaching the new curriculum effectively will require nontraditional pedagogy. Can enough teachers be trained to successfully implement inquiry-based, student-centered classes and labs that include quantitative reasoning? What new professional development initiatives are planned to meet this need? And will the increased need for professional development restrict access to the new program for schools with fewer resources, which is another concern of the NRC panels?

If the new curriculum can be successfully implemented, it may raise an additional question for colleges and universities, especially those serving large numbers of students. Will graduates of the new AP biology put up with the large-enrollment, fact-oriented, instructor-centered, lecture-based biology courses currently offered in so many of these institutions? An intriguing possible outcome of the AP revision is that it may eventually drive much-needed change in college and university teaching of introductory biology.

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PHYSIOLOGY

Unraveling Traveling

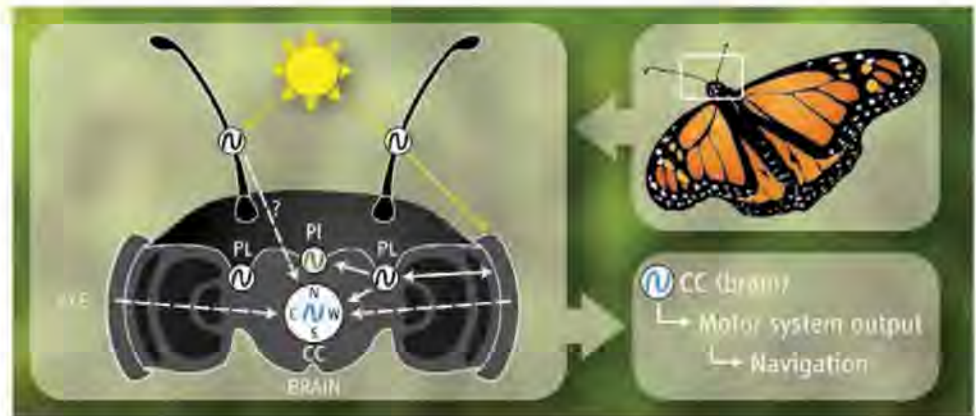
Charalambos P. Kyriacou

There are few more awesome sights in the animal world than the seasonal mass migrations of the monarch butterfly, *Danaus plexippus*, from the northern United States and southern Canada to its overwintering grounds in central Mexico (1). As with other insect orientations, the monarch uses the position of the Sun to calculate where it should be going. However, as the Sun moves across the sky during the day, the monarch must continuously adjust its calculations, which it does by using its 24-hour circadian clock. So where is this time-compensated clock located? On page 1700 of this issue, Merlin *et al.* reveal that it's in the antennae (2).

The monarch's ~3200-km journey is initiated by a photoperiodic response to the shorter daylengths of the fall, whereby the individual moves into a reproductive diapause to conserve resources, enhance longevity, and carry it through to the following spring. Then, after mating, eggs are laid in milkweed, and the few survivors and the new generation begin their journey home, laying eggs progressively further northward with the advancing growth of milkweed. After two or three such nomadic generations, the butterfly reaches its northern home, before the cycle begins again in the fall (1).

If the circadian clock is disrupted by environmental manipulations, such as constant bright light or phase-shifting of the light-dark cycle (12 hours:12 hours) by a few hours, the monarchs get lost (3). Merlin *et al.* observed that after surgical removal of the antennal flagellae, the butterfly's normal southwestern orientation is lost, even though the brain's canonical circadian clock keeps normal time (as indicated by the abundance of clock molecules during 24-hour cycles). In the intact animals, these molecules—*period*, *timeless*, and *cryptochrome2*—also keep time in the antennae with the same phase as in the brain. Even when explanted, the antennal clock keeps on ticking and can be reset by light, thereby maintaining a precise synchrony with the environmental light-dark cycle.

This light-dependent resetting of the antennal clock was challenged by blackening the antennae with enamel paint and maintaining the butterflies for >10 days in light-dark



The monarch antennal clock. Circadian clocks are located in the antennae, pars lateralis (PL), and pars intercerebralis (PI). Retinal photoreceptors that respond to polarized light connect to the PL clock through neuronal fibers expressing the clock protein CRY1 and to the central complex (CC) in a clock-independent pathway. CRY1-expressing fibers connect the PL and PI clocks, whereas CRY2-expressing fibers connect the PL and CC clocks. The putative Sun compass resides in the CC and connects to the motor output. A key question is whether the antennal clocks are directly connected to the CC Sun compass.

cycles (thus, only the antennae are effectively under constant darkness). Under these conditions, the antennal clocks started to drift and their molecular cycles were dampened. However, the brain clocks maintained their synchrony with the light-dark cycle, underscoring the independence of the two oscillators. Monarchs whose antennae were covered in clear enamel paint had no such problems, with antennal and brain clocks maintaining the same phase in light-dark cycles. In flight orientation tests, the clear-painted animals gave the expected southerly flight, whereas the blackened butterflies flew predominantly in a northerly direction. This ~180° shift in direction in the blackened monarchs would be expected if the clock free-ran in the dark with a period either 1 hour shorter or longer than 24 hours, because after 12 to 14 days of the experiment, these animals' antennal clocks would be in approximate antiphase (180°) relative to those that were entrained to the light-dark cycle. Indeed, the free-running endogenous eclosion rhythms of these butterflies are closer to 23 hours than to 24 (4). Consequently, the blackened monarchs revealed that their phase-shifted but functioning antennal clock dominated any navigational input into the time-compensated "Sun compass" that might come from the brain clock.

The antennal clock is therefore rather like a standalone global positioning system that one might use while driving, which now eclipses the paper map (brain clock). This result is surprising, given that several studies have set the

The monarch butterfly uses a time-compensated clock in its antennae to calculate seasonal migration routes relative to the Sun's position.

stage for a brain clock to mediate navigation. Monarchs have polarized light receptors in the dorsal rim area of the retina and these are connected to the presumed "clock" region, which is represented by four neurons in the pars lateralis (PL) of the brain (which express cycling clock molecules) (5, 6) (see the figure). Neuronal fibers from the PL that express CRY1 [which is encoded by the gene *cryptochrome*, the ortholog of *cry*, the circadian blue light photoreceptor of the fly *Drosophila melanogaster* (7)] extend to the optic medulla, where axons of the dorsal rim photoreceptors terminate, which suggests a putative circadian modulation of polarized light input (6). Other neurons that express CRY1 connect the PL with neurons of the pars intercerebralis (PI), another clock gene-expressing region (6) that has been implicated in diapause and aging in *Drosophila* (8)—clearly important phenotypes for monarch migration. CRY2-expressing neuronal fibers that may arise from the PI and PL are also found in the central complex (CC) region of the brain, where this canonical clock molecule shows rhythmic oscillations in expression (4). In locusts, polarized light information from dedicated photoreceptors is integrated into the CC, which is believed to house the Sun compass (9). Thus, all the connections are present in the monarch for a brain clock in the PL to connect to skylight photoreceptors, to diapause, and to the putative Sun compass in the CC—a putative migratory network. Yet the antennal clock appears to override any input from the brain clock for naviga-

tion. However, much of this network is dedicated to aspects of migration (e.g., reproductive diapause and longevity) that are regulated separately from navigation (10).

It may be that the CRY2-expressing neurons of the brain clock (PL) that connect to the CC are a red herring in terms of navigation, and these are simply there to mediate the diurnal rhythmic flight patterns of the butterflies. In *Drosophila*, locomotor activity is maintained by the CC (11) that, intriguingly, receives input from nonclock neurons that express CRY (12). Clarification of how the monarch antennal

clock connects to the putative Sun compass in the CC is certainly required. The possibility that antennal clocks are used in similar ways in other insects that use Sun compass orientation should also be entertained. Finally, *Drosophila* CRY behaves as a putative magnetoreceptor (13, 14), with the clear implication that these molecules could provide additional orientation cues for butterfly migration.

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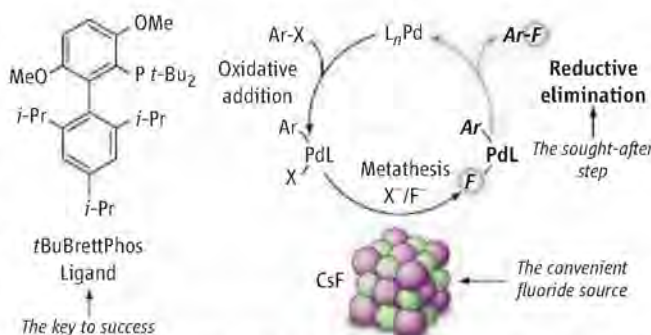
CHEMISTRY

A New Departure in Fluorination Chemistry

Véronique Gouverneur

Medicinal chemists often consider fluorine substitution of aromatics as a strategy for lead optimization, because the introduction of fluorine helps to rapidly improve pharmacokinetic and toxicological properties (1). Moreover, "editing" a lead structure with fluorine substitution can improve binding efficacy and selectivity. Traditional methods such as halogen exchange or diazonium-based transformations usually require reaction conditions that are too harsh for many aromatic molecules. These considerations have fueled interest in methodologies that are tolerant to functional group diversity, enabling fluorination of aromatics late in a synthetic sequence. On page 1661 of this issue, Watson *et al.* (2) report a novel palladium-catalyzed reaction that can be used to fluorinate a wide range of aromatics.

The recent success of transition metal catalysis for carbon-heteroatom bond formation suggests that the use of organometallic complexes for C–F bond construction could be central to future synthetic fluorine chemistry. Several laboratories have contributed to the development of metal-mediated fluorination to create aryl fluorides (ArF). It became quickly apparent that the most difficult elementary reaction of a transition metal-catalyzed process for aryl fluoride formation is the reductive elimination step, an event that releases the reduced metallic catalytic species and the product from the organometallic complex.



A new route to aryl fluorides. Reductive elimination from LPd(II)Ar(F) complexes has failed for many years as a route to aryl fluorides. Watson *et al.* solved this problem by using *t*BuBrettPhos as the ancillary ligand to force Ar–F bond formation; CsF is used as the fluoride source. The method may yield products with applications in pharmaceutical research and imaging.

In search of the elusive C–F reductive elimination event, Hull *et al.* (3) and Furuya and Ritter (4) used Pd(IV) intermediates to construct Ar–F bonds. These transformations (not always catalytic in palladium) used an electrophilic source of fluorine (F^+) as the oxidant. These studies were viewed as a major advance, even though the use of F^+ -type reagent might be restrictive. In earlier studies, Grushin (5) prepared $\text{L}_n\text{Pd(II)Ar(F)}$ complexes from a nucleophilic fluoride (F^-) source, but reported complications with the reductive elimination step necessary to form the Ar–F bond. Yandulov and Tran documented the formation of *p*-fluoronitrobenzene from a dimeric 16-electron Pd(II) complex; however, the low yield (10%) and the failure to extend this chemistry to unactivated or electron-rich aromatics cast doubt on whether the product resulted from reductive elimination (6).

A method for fluorinating a wide range of aromatic molecules will find immediate application in pharmaceutical research and may facilitate access to medical imaging reagents.

Reasoning that dimeric Pd complexes may impede aryl fluoride formation, Watson *et al.* have now prepared the monomeric complex LPd(II)Ar(F) —where L is the easily accessible ligand BrettPhos (see the figure)—and show that this complex remains monomeric in solution. The new complex finally enabled the sought-after reductive elimination step, delivering the desired aryl fluoride (see the figure). A catalytic variant (Pd pre-catalyst and BrettPhos) was also successfully implemented with AgF as the fluoride source, and control experiments ruled out other possible mechanisms.

Through further fine-tuning of the experimental conditions, the authors show that *t*BuBrettPhos is the ideal ligand for fluorinating aryl triflates (functional group CF_3SO_3), using CsF or spray-dried KF as the fluoride source. These data indicate that the correct choice of ligand is decisive for a successful outcome, allowing for the preparation of aryl fluoride from a stabilized 14-electron Pd(II) complex. The steric size of *t*BuBrettPhos may also compress the ArPdF angle, thereby forcing reductive elimination by bringing closer the aryl and fluorine substituents.

The chemistry reported by Watson *et al.* provides access to fluorinated heteroaromatics, as well as various aromatics with

electron-withdrawing substituents. Aryl triflates with electron-rich substituents required higher temperatures and in some cases led to the unexpected formation of regioisomeric products (isomers that differ in the location of functional groups within the molecule) when the reaction was performed in toluene. These undesirable competitive pathways, which are likely Pd-mediated, were suppressed by replacing toluene with cyclohexane. Functional motifs not compatible with the method are *ortho*-positioned Lewis basic groups.

Despite these limitations, the method reported by Watson *et al.* is a breakthrough in many respects, not least because it adds to our understanding of the catalytic chemistry of C–F bond formation. The ability to construct aryl fluorides from readily available fluoride salts is a major advantage, especially for applications beyond research and development. If future work allows for further optimization (catalyst loading or sensitivity

to water), the new process might rival both the Balz-Schiemann reaction, which uses hazardous reagents, and halogen exchange reactions, which are limited to electron-deficient precursors.

Another field that could benefit from this new reaction is positron emission tomography (PET), a molecular imaging technology commonly used to detect diseases. Drug developers also value PET as a tool for pharmacokinetic and pharmacodynamic evaluation at an early stage of drug development. ^{18}F -aromatics are a common motif in radiotracers, but to date, only a limited range of reactions is available for their preparation. Given the ^{18}F half-life of 109.7 min, the radiosynthesis, purification, and formulation of the ^{18}F radiotracers must be done as quickly as possible. Preliminary work by Watson *et al.* indicates that their method reduces the reaction time for the fluorination of naphthyl triflate to 30 min. With further optimization, the new chem-

istry may be a major step forward to access ^{18}F aryl fluorides, because radiochemists are averse to reactions using high-specific activity (SA) ^{18}F fluoride; lack of access to high-SA F^+ -type reagents is one of the key problems in the field.

The study by Watson *et al.* constitutes a new departure in fluorine chemistry not limited to aryl fluoride. It offers a tantalizingly diverse range of potential extensions and applications. So, let's roll up our sleeves and get back to work!

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CHEMISTRY

Tin Takes Ethylene On—and Off

Lawrence R. Sita

Unexpected results can force the reevaluation, refinement, or rejection of scientific theories that seemed firmly supported. In organic chemistry, a well-established set of rules based on the symmetry of molecular orbitals can predict whether reactants with double or triple bonds will form cyclic products. On page 1668 of this issue, Peng *et al.* (1) now report the highly efficient, simultaneous addition of two molecules of ethylene ($\text{H}_2\text{C}=\text{CH}_2$) to a tin analog of acetylene: a distannyne, $\text{RSn}\equiv\text{SnR}$, where the R groups are bulky hydrocarbons. This reaction occurs despite what on the surface appears to be the breaking of simple symmetry rules. More remarkably, the reaction can be reversed with only small changes in pressure and temperature. In organic synthesis, similar reactions create very stable cyclic products.

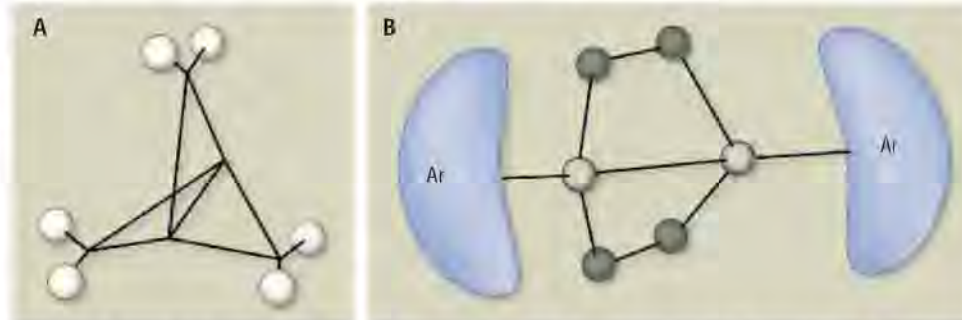
It can be tempting to dismiss these findings as a chemical curiosity that arises when carbon atoms are replaced by one of the heavier elements in its group, which include silicon, germanium, and lead as well as tin. In fact, the present results reveal much about the health of modern qualitative valence-bond theo-

ries. In these approaches, the set of molecular orbitals formed from the valence-shell atomic orbitals are determined by simple application of group theory (2, 3). Chemical reactivity is associated with the “frontier” molecular orbitals, the highest occupied and lowest unoccupied energy levels. Electronic redistributions that would occur in a reaction are either allowed or forbidden on the basis of symmetry, which takes into account that the spatial electron density distribution, or “lobes,” of p

A tin analog of acetylene can perform reactions normally forbidden to acetylene: It can bind two ethylene molecules in a reversible fashion.

and d orbitals have positive or negative phase, as well as limits on orbital occupancy by electrons. For example, the Woodward-Hoffmann rules use orbital symmetry to predict whether a ring-closing (cyclization) reaction will occur in a single step, and whether the reaction will occur thermally or require photoactivation so that it proceeds through an electronically excited (higher-energy) state (4).

The reactions described by Peng *et al.* follow what has been a successful strategy in



Benchmark molecules bend the rules. A number of organic molecules, as well as molecules that include carbon's heavier analogs such as tin, have forced rethinking of the simpler rules of chemical bonding and reactivity based on molecular orbital symmetry. (A) Wiberg and co-workers (9) synthesized [1.1.1]propellane, which has two “bridgehead” carbons linked by three $-\text{CH}_2-$ groups. The normally tetrahedral bonds at these carbons are bent back into an inverted umbrella pattern. (B) Peng *et al.* synthesized a tin analog of acetylene in which each tin atom (shown in gray) bears a single but bulky hydrocarbon group. Unlike acetylene, it can add two ethylene molecules at ambient conditions and will liberate them simply by placing the product under vacuum.

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chemistry for establishing new benchmarks that test the limits of these bonding theories, by synthesizing molecules that appear to defy generally accepted rules governing bonding. More specifically, these rules describe the extent and nature of overlap of electron density associated with atomic orbitals that contribute to the formation of stable molecular structures (5, 6). For example, the valence s and p orbitals of carbon have similar energies, so they tend to mix according to symmetry requirements to produce a lowest-energy tetrahedral geometry for the four single bonds of carbon atoms. In highly “distressed” (7) or “nonclassical” (8) organic molecules, such bonding arrangements are severely distorted away from tetrahedral geometries to such an extent that the resulting higher energy of the molecular framework would have been thought impossible to achieve. Successful syntheses of nonclassical molecules can also provide examples of potential new reaction pathways for subsequent synthetic transformations.

A seminal contribution to the advancement of modern theories of structure and bonding was made by Wiberg and co-workers [reviewed in (9)]. They predicted the stability of [1.1.1]propellane, a highly strained C_5H_6 hydrocarbon that fuses three rings (see the figure, panel A), and went on to synthesize this molecule under ambient conditions and validate its structure in experimental studies. The formal valence-shell orbitals describe bond paths that require an “inverted umbrella” geometry for the bridgehead carbon atoms that link the rings, which greatly increases the strain energy associated with this molecular framework.

Before attempting the synthesis of such daunting targets, most chemists would want some assurance that the target is actually stable enough to isolate or observe spectroscopically. Predictions of stability (5–9) for these nonclassical molecules can now be assessed quantitatively because of advances in computational methods, which include *ab initio*, semiempirical, and density functional theory. In these methods, the electronic distributions that define atomic positions and bond paths within a molecule are not biased by the artificial construct of isolated molecular orbitals, and the stability of more complex bonding arrangements can be successfully probed and rationalized (10).

The work of Peng *et al.* is also related to efforts that refine fundamental concepts of structure and bonding through the computational investigation, synthesis, and characterization of molecules in which the carbon is replaced by the heavier group 14 elements (11). The issue is whether these benchmark

molecules can be viewed as “heavy-atom analogs” that follow the same set of bonding and reactivity rules as all-carbon-based organic molecules, or whether their properties require a rethinking of orbital interactions that can better describe differing behavior in structure, bonding, and reactivity. Ironically, a dearth of synthetic methods has led to the discovery of new benchmark molecules and reactions for these heavy-atom analogs, mainly through serendipity. Often, each new discovery has also challenged reconciliations with theory.

By all initial appearances, the forward and reverse chemical processes reported by Peng *et al.* do not conform neatly with what we would expect on the basis of their carbon counterparts. The Woodward-Hoffmann rules predict that cycloaddition of $H_2C=CH_2$ to a substituted acetylene ($RC\equiv CR$) should be a forbidden process. Similarly, the stability of bicyclo[2.2.0]hexane (BCH), the simplest analog to the product reported by Peng *et al.*, is quite different (see the figure, panel B). Furthermore, the Woodward-Hoffmann rules would predict that the reverse fragmentation of BCH should follow an entirely different ring-opening pathway than that observed for the tin-containing product, 1,4-distannabicyclo[2.2.0]hexane (DSBCH).

One way in which symmetry-based orbital overlap arguments must be refined for carbon’s heavier counterparts is that s and p orbitals tend to be further apart in energy and mix more weakly. Valence bonds

are often then made from orbitals with much more p character, and bond angles closer to 90° are more commonly seen. Fortunately, a successful reconciliation of the present observations may not require that any new conceptual models of bonding be invoked for DSBCH.

Further high-level computational investigations of this system will also undoubtedly lead to a better understanding of the changes in free energy for the forward and reverse processes that establish DSBCH as only a “minimally stable” molecule. However, it is the facile nature of the forward and reverse concerted cycloaddition of two $H_2C=CH_2$ with one $RSn\equiv SnR$ that opens a new, currently blank, chapter describing modern theories that govern structure, bonding, and fundamental chemical processes that we have yet to envision.

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CHEMISTRY

Emergent or Just Complex?

Anna C. Balazs¹ and Irving R. Epstein²

Efforts toward creating artificial cells are shedding light on how life may have emerged.

The concept of emergence in the physical and biological sciences is an elusive one. The term refers to phenomena in which the complexity of structures or behaviors in systems with many interacting components exceeds that predicted from knowledge of the individual components and the forces between them. A recent conference (1) provided an opportunity to probe the notion of emergence from a wide range of viewpoints, loosely linked by the themes of

increasing complexity and molecular organization. The scope of the conference is exemplified by S. Rasmussen’s characterization of hydrogen as “a colorless, odorless gas, which, given enough time, turns into people.” Perhaps the prototypical emergent phenomenon is the origin of entities that can plausibly be called alive (2). How does one get from atoms to simple molecules to systems that can grow, reproduce, metabolize, move, and adapt?

Carbonaceous meteorites (3) may offer a glimpse into the organic chemistry of presolar environments that resulted in the production of the first chiral amino acids, which may have served as early building blocks and/or as asymmetric catalysts. However, many steps

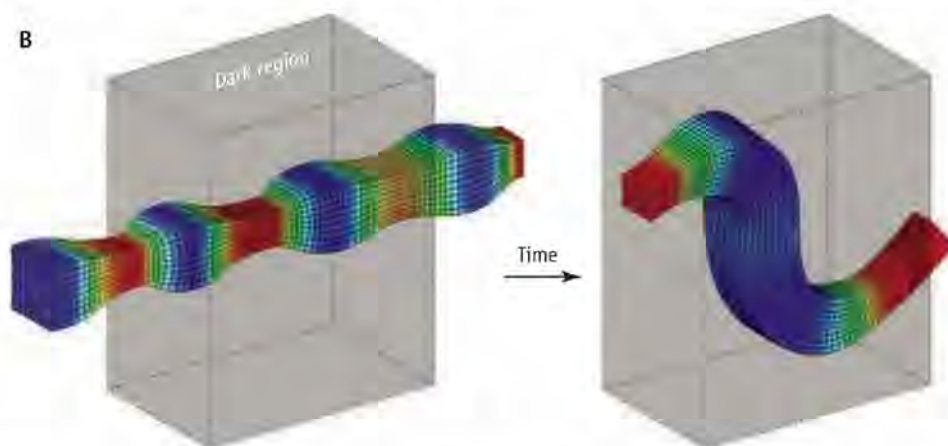
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from these amino acids to living cells remain to be elucidated. For example, how did small monomers polymerize into longer chain species, such as nucleic acids (4), and how were the developing reaction networks compartmentalized into protocells (5)? None of these processes contradicts or is inherently incomprehensible in terms of our current understanding of thermodynamics, chemical kinetics, and catalysis. Yet, a coherent, explanatory, conceptual synthesis is far enough away that it still seems reasonable to characterize early life as emergent.



Spirals and worms. (A) Segmented spirals emerge from about one million interacting nanodrops of aqueous BZ solution in an oil-water microemulsion (15). Frame size, $3.72 \times 4.82 \text{ mm}^2$. (B) In a simulation (16), a BZ gel “worm” autonomously reorients itself to localize in the dark region.



One popular example of emergence is Conway’s “Game of Life” (6). In this game, a rectangular grid of sites is populated by “cells.” A simple set of rules determines whether those cells live, die, or multiply, based on the number of neighboring sites that are populated. Depending on the rules chosen and the initial conditions specified, repeated iteration yields a remarkable variety of moving and stationary patterns that seem far more intricate than the simple elements and rules of the game should allow. This game is a simple example of cellular automata (7), whose richness continues to surprise.

More generally, computer programming provides an attractive metaphor for emergent behavior in chemical and biological systems. If one imagines molecules and reactions as analogous to the primitive operations and instructions in a programming language, one can build complex chemical “programs” to accomplish specified tasks. Because molecules, such as the complementary base pairs in DNA, can have natural affinities for one another without forming covalent bonds (8), much of the “work” of this sort of programming occurs very efficiently via self-assembly. Complex supramolecular structures can be designed from DNA “origami” seeds and

tiles (9). Deoxyribozyme-based molecular automata can play tic-tac-toe (10).

Even relatively simple chemistry can yield a remarkable array of dynamic behavior resembling that displayed by multicellular organisms. For example, when a few dozen nickel electrodes undergoing electrodisso- lution are coupled to each other, they form a small set of clusters that oscillate in phase with one another, resembling behavior seen in brain slices (11). Another system, catalyst-impregnated beads in a solution containing the reactants of the Belousov-Zhabotinsky

more, simulations have shown that light can be used to direct the movement of a small BZ gel “worm” (see the figure, panel B) (16).

It may also be possible to exploit recent synthetic advances to direct the conglomerates to fight or flee—two other hallmarks of biological entities. For example, magnetically driven microspheres at liquid-liquid interfaces can be manipulated such that some microspheres raid and attack others, resulting in the formation of larger snakelike figures (17). Under certain conditions, these snakes divide into smaller entities, thereby

(BZ) reaction, displays the phenomenon of “quorum sensing,” when the bead density reaches a critical value, the population of independent, quiescent beads undergoes a sharp transition to coherent oscillation (12). Biomolecules—notably proteins and nucleic acids—provide particularly impressive examples of emergent phenomena. Networks of such molecules can perform functions analogous to associative learning (13).

The various threads of the above research could provide useful guidelines for creating artificial cells that can simultaneously perform multiple functions, such as self-propulsion, self-sensing, and a form of communication that leads to cooperative activity. Researchers have designed self-propelled microscopic “swimmers” and colloids and identified conditions where hydrodynamic interactions between these objects drive them to swim together in a concerted manner (14). Such self-propelled entities could exhibit greater “intelligence” if they incorporated some internal chemical dynamics, such as provided by the BZ reaction. In the case of the oscillating beads (12) and that of microemulsions consisting of nanodrops of aqueous BZ solution suspended in an oil phase (15), the state of one entity affects the behavior of the rest, and, in this respect, different units communicate with each other (see the figure, panel A). Further-

undergoing a simple form of reproduction.

Finally, advances in manipulating DNA (9) may be harnessed to further direct such “intelligent” microscopic objects. For example, functionalization of colloid particles with complementary strands of DNA (18) leads to a new class of synthetic materials designed to self-replicate and, as a result, grow exponentially. Coupling this technology to beads that communicate, fight, flee, and consume energy would open the door to objects displaying essential hallmarks of living systems.

The notion of emergence as an area of scientific inquiry is inherently paradoxical, in that emergent phenomena are defined as those whose origins we do not completely understand. As we probe more deeply, what is perceived to be emergent necessarily recedes into the distance as we begin to see more clearly how interactions between components give rise to more complex structures and behaviors. Nonetheless, how life emerged from atoms and molecules is a question that, whatever we choose to call it, will challenge scientists for many years, if not centuries, to come.

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MATERIALS SCIENCE

Simulating Multifunctional Structures

Simon R. Phillpot and Susan B. Sinnott

More powerful computers and better algorithms are making it possible to probe and engineer the atomic-level properties of nanostructures.

Electronic devices, sensors, and electromechanical systems are now reaching nanoscale dimensions at which they contain only hundreds of millions to billions of atoms. Developments in materials simulation, driven by algorithmic advances and rapid increases in computer power, now allow systems of tens of millions of atoms to be routinely simulated, while systems of billions of atoms can be simulated on the largest supercomputers (1). This is leading to new capabilities in interfacial engineering design, development of nanostructures with prescribed properties, tuning of functionality under typical or extreme conditions, and prototyping of nanostructures in silico.

The key missing piece to such device-size simulations has been flexible and powerful descriptions of interatomic interactions that allow materials of different bonding types (metallic, covalent, and ionic) to be treated in an integrated manner. On the one hand, mesoscopic and continuum-level modeling methods are not designed to reach down to the atomic dimensions at which discrete physical and chemical processes take place. On the other hand, electronic structure methods have long been able to simulate heterogeneous systems; indeed, they provide the highest materials fidelity of currently available simulation methods (2). However, because they treat the electronic degrees of freedom of the system explic-

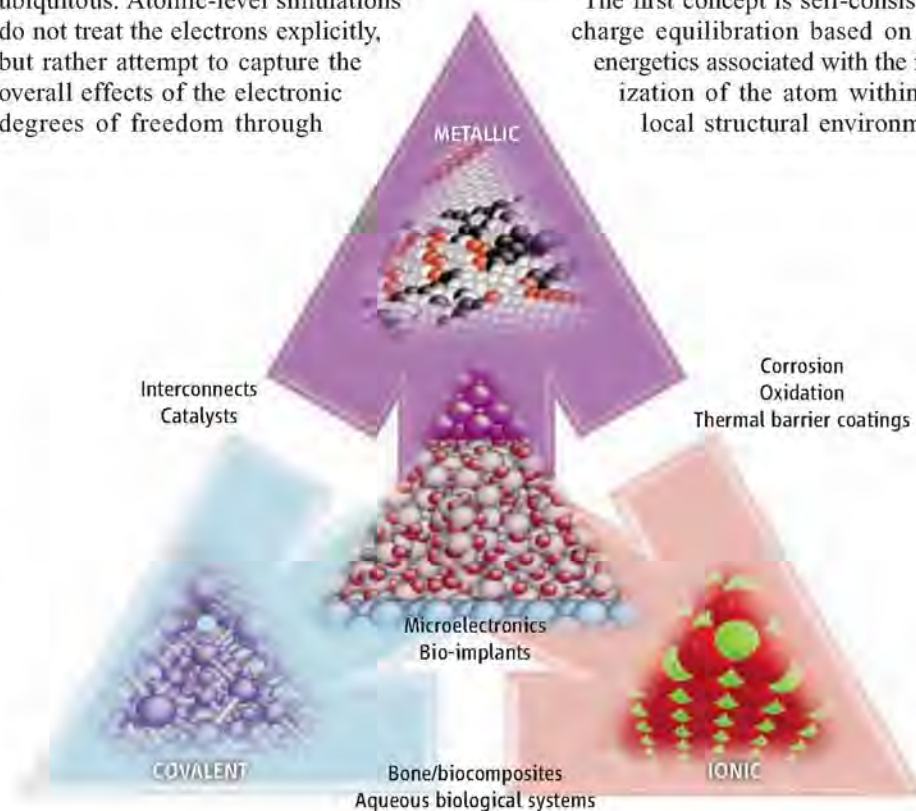
itly, they are computationally expensive and cannot reach up to the scale of many experimental nanostructures. The gap between these two approaches is filled by atomic-level simulation methods, of which classical molecular dynamics simulation is the most ubiquitous. Atomic-level simulations do not treat the electrons explicitly, but rather attempt to capture the overall effects of the electronic degrees of freedom through

effective interatomic interactions among the atoms and ions in the system.

The very different physics and chemistry associated with metallic, covalent, ionic, and van der Waals bonding have led to the development of very different paradigms for the encapsulation of these electronic effects in atomic-level simulations (see the figure). Within its own domain of materials, each has proved very successful: for example, the embedded atom method (EAM) describes a broad range of structural phenomena in metals (3). Similarly, fixed-charge approaches have been used successfully to model ionic solids (1) and biomaterials in aqueous environments (4). However, the approaches for different bonding types are so different that it has not been easy to establish whether, or how, a single framework could capture them all in the absence of a self-consistent electronic structure treatment.

Nevertheless, such a framework has now emerged and is opening up the possibility of simulating structurally and chemically complex nanostructures and nanoscale processes. This framework is built on two key concepts, which in combination appear to provide the power and flexibility to describe the effects of complex electronic-level behavior without simulating the electrons themselves.

The first concept is self-consistent charge equilibration based on the energetics associated with the ionization of the atom within its local structural environment



The modelers' playground. Many of the most challenging and important applications of materials involve interfaces between disparate bonding environments. The ability to simulate such interfaces promises new capabilities in computationally prototyping nanostructures or devices at experimental length scales.

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(5). A strong indication that this could be applied to systems with mixed bonding types came when it was combined with the EAM method to simulate interfaces between metallic Al and Al_2O_3 , in which an Al atom in the metal remains charge neutral but gathers an ionic charge in the oxide phase (6).

The second concept is that of the autonomous, self-consistent determination of the bonding type: metallic, covalent, or ionic, or a combination thereof. It is now clear that the idea of the bond order has this capability. The bond order essentially measures and regulates the number and strength of the bonds among atoms. It was first incorporated in a computational approach more than 20 years ago for covalently bonded diamond and silicon, and then further developed with great success for covalently bonded carbon-based materials in the reactive empirical bond order (REBO) method (7). The first hint that the bond order approach could be more generally applicable came when Brenner showed that REBO is formally identical in the appropriate limit to the EAM potential for metallic systems (8).

The two concepts of charge equilibration and the bond order approach were brought together by Yasukawa (9, 10), who was then able to explore the structure of interfaces between metals and ionics, and between metals and covalent materials. In the context of

applications in microelectronics, oxide-metals systems, and oxide-semiconductor interfaces, this approach has been shown to describe metals such as Cu and the Si/ SiO_2 system, including the correct phase order of the tetrahedrally coordinated phases of Si (11). The most fully-developed approach that brings these two concepts together is the ReaxFF (reactive force field) method, which has been implemented for a number of organic and inorganic systems and successfully used to attack problems that require accurate modeling of chemistry, including oxidation, tribochemistry and evolution of materials in aqueous environments (12, 13).

The current approaches indicate that the paradigms of charge equilibration and bond order can describe the full range of bonding types operating in a wide range of systems. However, formidable challenges remain. First, it is important, but difficult, to maintain complete transferability of the interactions: that is, for a robust, fully general method it is essential for the description of, for example, oxygen-oxygen interactions to be the same in all systems. Second, the development of functional forms and parameter sets for the interatomic interactions presently has to be carried out on a case-by-case basis, a costly process in terms of computer and human resources. Third, as is the case with all empirical approaches, the methods are highly dependent on the quality

of the data sets used in parameterization.

It is becoming increasingly clear that while methods for simulating multifunctional materials structures are still undergoing rapid development, they show enormous promise for modeling complex, multifunctional materials, when used either alone or together with mesoscale and electronic-structure methods. We will thus soon be able to probe a wide range of nanoscale structures and phenomena with unprecedented control and flexibility on the length scale at which they exist and operate in the real world.

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CELL BIOLOGY

Evolving Cell Signals

Mark O. Collins

Protein phosphorylation has emerged as a ubiquitous regulatory switch in cell signaling networks. Improved methods to purify and characterize phosphopeptides have led to an explosion of phosphorylation site data, and we can now explore how protein phosphorylation evolved. This question has been tackled by two studies in this issue. On page 1686, Tan *et al.* (1) report that tyrosine residues (which can be phosphorylated) have been selectively lost through metazoan evolution. On page 1682, Holt *et al.* (2) show that most phosphorylation sites shift position in rapidly evolving, disordered regions of proteins.

Protein phosphorylation is controlled by hundreds of enzymes (kinases and phosphatases). Together with the estimated several

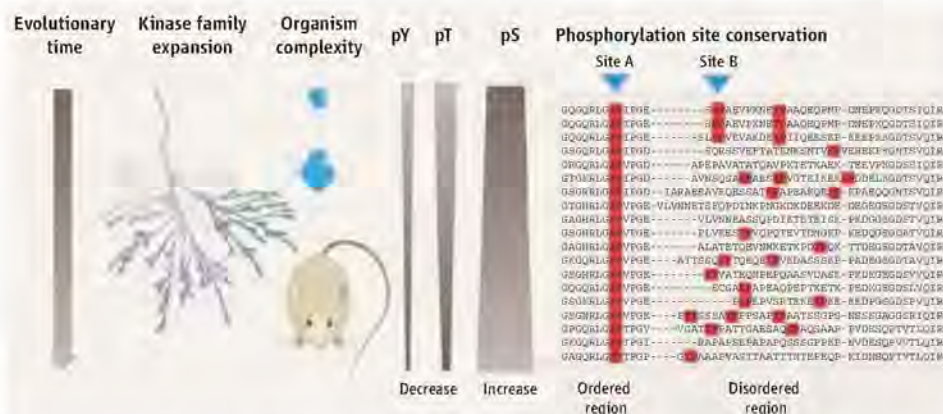
hundred thousand phosphorylation sites in the human proteome (all proteins encoded by the genome) (3), phosphorylation represents a large combinatorial repertoire for proteome regulation. The position of phosphorylation sites in proteins is determined by primary structure and by kinase and phosphatase substrate specificity, which has evolved over hundreds of millions of years (4). This specificity is under selective pressure to maintain beneficial and remove deleterious phosphorylation sites (5).

What makes some phosphorylation sites useful and others detrimental during evolution? This may be explained, in part, by looking at phosphorylation in terms of protein structure. Proteins are generally either folded into ordered structural domains, disordered with little tertiary structure (unless bound to other proteins or DNA or RNA molecules), or contain ordered domains separated by disordered

Cell signaling may be understood in terms of the evolution of the topology and distribution of protein phosphorylation sites.

protein loops. Ordered regions are usually catalytic, structural, or are protein interaction domains, and therefore have been evolutionarily constrained by structure-function requirements. Disordered regions, however, have evolved rapidly (6), contain many short linear motifs that mediate protein-protein interactions (7), and have numerous phosphorylation sites compared to ordered regions (8, 9). These sequences represent "hot spots" for regulation by phosphorylation, as well as hubs for protein interactions (10). Both domain types are specified by their residue compositions. In particular, disordered sequences are enriched in serine and threonine residues, whereas ordered sequences are enriched in tyrosine residues (11, 12), highlighting functional differences in these types of phosphorylation. Therefore, order, disorder, and phosphorylation are intimately linked, but little has been known about how these features evolved.

Proteomic Mass Spectrometry Group, The Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK. E-mail: moc@sanger.ac.uk



Phosphorylation selection. As protein kinases evolved and species complexity increased, the numbers of genomically encoded tyrosine residues [and thus phosphorylated tyrosines (pY)] decreased proportionally. This negative correlation also applies to threonine (pT) but not serine (pS) residues. Positionally conserved phosphorylation sites tend to be located in ordered protein domains, whereas those not conserved are located in intrinsically disordered regions where their exact positions shift with evolutionary time.

To identify phosphorylated substrates in yeast, Holt *et al.* used a cyclin-dependent serine-threonine kinase (Cdk1) that was genetically modified to be inhibited by a small molecule. They defined Cdk1 phosphorylation sites by adherence to the minimal Cdk1 phosphorylation consensus sequence and by a 50% reduction of phosphorylation site abundance caused by inhibitor treatment. This approach identified 547 unique phosphorylation sites on 308 candidate Cdk1 substrates. Although the method may have biased against sites not under tight control by phosphatases, the substrates identified were defined with high confidence.

In agreement with another study (9), most serine-threonine phosphorylation sites were located in disordered regions and were clustered in the primary amino acid sequence. Comparing these sites across 32 fungal species revealed little positional conservation. Indeed, high turnover of Cdk consensus sites has been reported across a wider evolutionary set of 21 species (13), and rapid evolution of phosphorylation sites was found between human and model organisms (3). Holt *et al.* found a few positionally conserved phosphorylation sites in more ancient proteins. These are expected to drive precise conformational changes and therefore evolve more slowly. Other work has shown that evolutionarily conserved phosphorylation sites are more likely to be located in ordered protein domains as well as being enriched in nuclear and cancer-associated proteins, highlighting a role in the ancient process of cell division (3).

In contrast to previous proposals (14), Holt *et al.* suggest that the exact location of nonpositionally conserved phosphorylation sites may not be important, especially in the context of phosphorylation-dependent

interactions. Proteins that bind to phosphorylated sites have to some extent degenerate specificity requirements for sequences flanking the sites and, hence, could bind to a site that has shifted position in a disordered region. Holt *et al.* found that many Cdk1 substrates were binding partners of 14-3-3 proteins in yeast. These substrates contained multiple phosphorylation consensus sites clustered together and, because 14-3-3 proteins are typically dimers, their interaction with multiphosphorylated sequences would be of higher affinity compared to single phosphorylation sites. The evolutionary plasticity of phosphorylation sites in disordered regions, combined with the tolerance to change by domains that bind to phosphorylation sites, may represent a mechanism to create generic phosphorylation-dependent interactions.

How does the evolution of tyrosine phosphorylation differ from that of serine-threonine phosphorylation? Tan *et al.* traced the occurrence and frequency of tyrosine phosphorylation in metazoans as the number of tyrosine kinases and distinct cell types (a measure of organism complexity) through time. A number of genomically encoded amino acids were negatively correlated to the number of distinct cell types. One of these amino acids is tyrosine, implying that metazoans with more cell types contain proportionally less tyrosine and, hence, fewer potential tyrosine phosphorylation sites (see the figure). Tyrosine content was also negatively correlated with numbers of tyrosine kinases and with the number of predicted phosphotyrosine binding domains, indicating that signaling specificity was maintained as metazoans acquired more tyrosine kinases as well as proteins that functionally respond to tyrosine phosphory-

lation. In addition, the energetic cost to an organism of producing an amino acid was shown not to be the driving force of tyrosine loss. Tan *et al.* propose that as new tyrosine kinases evolved by gene duplication, deleterious tyrosine phosphorylations arising from divergent kinase specificity were removed by a system-wide adaptive mechanism. Beneficial phosphorylation sites would be retained, but sites that negatively affected species survival were lost through mutations.

Threonine content was also negatively correlated with metazoan complexity as well as with numbers of serine-threonine kinases, whereas no such correlations were apparent for serine content. Perhaps this is because the local sequence environment of serine phosphorylation is important—disordered regions evolve rapidly and are more tolerant to extensive serine phosphorylation than are sequences in ordered domains. However, it is not clear how threonine phosphorylation in rapidly evolving disordered sequences fits with the selective loss of threonine residues in evolution.

That the exact position of serine and threonine phosphorylation sites may not be important will influence studies in which sites are individually mutated to ascribe function. It is likely that a more combinatorial view of phosphorylation will be needed to understand functional effects. Unlike the rapid evolution of serine-threonine phosphorylation-based signaling networks, phosphotyrosine signaling has been constrained during evolution to protect against aberrant signaling. This raises questions about whether tyrosine loss is more prevalent in certain classes of proteins or if some proteins exhibited selective tyrosine gain during evolution.

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EDUCATION

Experts Urge Bold New Undergrad Biology Courses for the 21st Century

Biology 101 must undergo a dramatic shift in its texts, teachers, and testing to prepare all students—not just science majors—for their futures in an increasingly scientific and technological society, experts said at a groundbreaking conference sponsored by the National Science Foundation (NSF) and AAAS.

Rote memorization is the rule in most classes, leaving many students unsure how scientists do their work and unable to evaluate scientific claims. But participants at the Washington, D.C., event offered innovative curricula and a renewed focus to develop these skills in their students.

“Realizing that the status quo in science education is not achieving the results we need, we have to undertake this bold challenge, breathing new life into our classrooms,” said NSF Director Arden Bement.

Tasks like memorizing the parts of a cell “and spitting back the answers on multiple-choice exams” are more common than critical-thinking exercises and hands-on experimentation, said Bruce Alberts, editor-in-chief of the journal *Science*. “It’s really taken all the joy and interest out of science education—it’s corrupted.”

The “Vision & Change in Undergraduate Biology Education” conference, held 15 to 17 July, marked the midpoint of an intensive 3-year effort by AAAS’s Education and Human Resources unit and NSF. In 2006, the organizations held a series of conversations with more than 200 faculty members, administrators, and undergraduate students, seeking input on how to improve the curriculum.

The conversations formed the basis for this summer’s conference, which drew 500 faculty members, education administrators, and policy-makers to discuss how to rebuild biology education into a pursuit as vibrant and relevant as the science itself.



In the field. Students in the NSF Research Experiences for Undergraduates participate in ongoing field studies as part of an innovative science curriculum.

“Right now, the biology we teach does not reflect the biology we do,” said Felicia Keesing, an associate professor of biology at Bard College.

Students want to know more about the connections and the applications of the science they learn, and they prefer interactive teaching methods. But for the most part, the current textbooks and testing regimes thwart this type of learning, Keesing said.

In plenary speeches and smaller working groups, the conference participants outlined the essential elements of a 21st-century biology course: hands-on research programs, more technology in the classroom, student-centered presentations and opportunities for teaching others, and communities of professors and students working on collaborative, often international projects.

Biology faculty should be prepared to expand and update their own education to accomplish these goals, said Carol Brewer, a conference co-chair and associate dean at the College of Arts and Science at the University of Montana. “Teaching methods

should be as innovative as the science taught in class,” she noted.

Alan I. Leshner, conference co-chair and AAAS CEO, said the conference was among the most important in his 30 years in Washington, D.C. But he cautioned the participants to be wary of solutions that might only support a scientific workforce while leaving behind most undergraduates. Leshner, who is also the executive publisher of *Science*, said all citizens need to understand how researchers work in order to make informed decisions in a world where “science is assuming a near-omnipresent role.”

Alberts and others pointed to the findings of a July survey by the Pew Research Center for the People & the Press and AAAS as a sign of how undergraduate biology education may be falling short. The survey’s results, which found significant divergence in how scientists and the public view the research on climate change and evolution, “struck me as a symptom of our striking failure” to share how scientific knowledge is developed and evaluated, said Alberts.

—Benjamin Somers and Becky Ham

AAAS PACIFIC DIVISION

San Francisco Bay: The Coming Flood?

SAN FRANCISCO—Humans have had a disruptive impact on San Francisco Bay since the days of the Gold Rush, with mining sediment, development, and industrial waste tainting waters and harming wildlife throughout the famous estuary. But now Bay researchers see the potential for human-caused change on an unprecedented scale as a result of the warming climate.

At the annual meeting of the AAAS Pacific Division here, top Bay experts detailed the current and future impacts of climate change on the complex Bay ecosystem, from the high peaks of the Sierra Nevada to the coastline outside the Golden Gate. The most pervasive threat, they said, could come from rising seas, with some models predicting Bay levels could rise by up to 140 centimeters (about 55 inches) by the end of the century.

That could inundate low-lying urban areas, including international airports in San Francisco and Oakland, and submerge tidal marshes that are essential to the Bay’s health. And with water levels already 20 to 30



Rising waters. Research by the U.S. Geological Survey and others shows that if water levels in the San Francisco Bay rise 140 cm by 2100, as some models predict, thousands of acres of tidal marsh and developed land (in blue) would be vulnerable to inundation.

cm higher than a century ago and a storm-spawning El Niño system emerging in the Pacific, this winter could foreshadow trouble ahead.

“Sea-level rise during the next El Niño could provide a preview of what sea level in the Bay will look like in the future,” said Dan Hanes, a U.S. Geological Survey (USGS) oceanographer and former professor of civil and coastal engineering at the University of Florida. “If there is a storm coincident with high tides anytime during an El Niño winter, there will be significant flooding in the region.”

The AAAS Pacific Division’s 90th annual meeting, from 14 to 19 August at the California Academy of Sciences and San Francisco State University, drew more than 475 scientists, engineers, teachers, students, journalists, and others. Marking the 150th anniversary of Charles Darwin’s *On the Origin of Species*, the meeting focused on how nature changes through evolution and how humans must build a sustainable relationship with nature to ensure the future health of all life.

But the events at the meeting included a diverse range of issues: the search on Earth and beyond for “weird life,” or life that does not share a biochemical heritage with known plants and creatures; project-based science learning; recent advances in pharmacology and toxicology; and communicating science to the public.

The AAAS Pacific Division, with 30,000 members, has long focused attention on the San Francisco Bay. In 1977, 1980, and 1994, the division held symposia on the estuary and produced reports that still provide valuable insight to today’s researchers. This year, at a day-long symposium, more than a dozen researchers from universities, government agencies, and non-governmental organizations depicted the Bay as dynamic and resilient, but under extraordinary stress.

Great progress has been made in reducing sewage discharges and the concentrations of many heavy metals, said Jay A. Davis, an environmental scientist at the San Francisco Estuary Institute. But mercury, dioxin, and polychlorinated biphenyls (PCBs) remain problems, and brominated fire retardants (PBDEs) have been found in Bay food webs at concentrations not seen elsewhere in the world, Davis said.

Tidal marshes and wildlife such as the endangered California Clapper Rail are slowly rebounding. At the same time, though, more than 250 invasive species—cordgrass, kelp, and clams, even goldfish and catfish—are establishing the Bay as “among the most invaded estuaries in the world,” said Edwin Grosholz, a benthic ecologist at the University of California-Davis.

Climate change could compound such

problems by stirring up Bay-floor sediment that contains toxicants and by making the Bay more hospitable to other invaders. And those, researchers said, are just some of the problems posed by the changing climate.

Noah Knowles, a USGS research hydrologist, explained that Bay waters could turn more salty if less precipitation falls in the Sierra Nevada as predicted by some climate models. More ominously, Knowles said that if Bay levels rise by a projected 50 to 140 cm, the threat to developed areas might compel policy-makers to consider improving existing protective levees and building new ones—at a cost of billions of dollars.

Outside the Golden Gate, Hanes reported, the reduced flow of sediment from the Bay may be related to the shrinking size of the Ebb Tide Delta, a radial-shaped underwater ridge that protects the coast. The shrinking ridge, combined with rising seas and bigger Pacific waves, may be contributing to significant, damaging coastal erosion.

SCIENCE POLICY

New AAAS Database Could Aid Voting Reform

With concerns persisting about the function—and malfunction—of the U.S. voting system, AAAS has launched the nation’s first Web-based, searchable database that provides access to a broad range of voting-related research.

The project will give researchers, election administrators, journalists, and others fast, free access to studies on issues ranging from voting technology and ballot design to voter behavior and impediments to voting. The database debuted with about 500 entries and is expected to grow considerably.

Worries about the voting system emerged after problem-plagued elections in 2000 and 2006. The National Science Foundation and AAAS convened scholars, election administrators, and others for a workshop in 2004; the Carnegie Corporation of New York and AAAS held another in 2006. Plans for a database emerged from those talks, said Mark S. Frankel, director of the AAAS Scientific Freedom, Responsibility and Law Program.

“There is a growing consensus in America that improvements to the election process are very much needed,” said Frankel, who oversees the database. “More research and greater understanding of the U.S. voting system are imperative in order to implement effective changes.”

Find the AAAS Research Database on the U.S. Voting System and Voting Technology at <http://votingtech.aaas.org>.

Oregon Teacher Wins AAAS Education Prize

Michael Lampert, a physics teacher in Salem, Oregon, is the winner of the 2009 AAAS Leadership in Science Education Prize for High School Teachers.

The West Salem High School teacher,

a former doctoral candidate in atomic physics, is a 20-year veteran who has transformed his classroom into a center of innovative teaching techniques. But one initiative set him apart: He trained his high school students to teach science to second graders, with the lessons based on state standards for science education. The prize committee praised that project as "the essence of good teaching."

In its third year, the AAAS Leadership in Science Education Prize for High School Teachers, supported by AAAS Fellow Edith Neimark, recognizes a high school teacher who has contributed significantly to the AAAS goal of advancing science education by developing an innovative and effective classroom strategy, activity, or program.

—Molly McElroy and Becky Ham

ELECTIONS

AAAS Annual Election: Preliminary Announcement

The 2009 AAAS election of general and section officers will be held in November. All members will receive a ballot for election of the president-elect, members of the Board of Directors, and members of the Committee on Nominations. Members registered in more than one section will receive ballots for elections for each section they are enrolled in.

Candidates for all offices are listed below. Additional names may be placed in nomination for any office by petition submitted to the Chief Executive Officer no later than October 26. Petitions nominating candidates for president-elect, members of the Board, or members of the Committee on Nominations must bear the signatures of at least 100 members of the Association. Petitions nominating candidates for any section office must bear the signatures of at least 50 members of the section. A petition to place an additional name in nomination for any office must be accompanied by the nominee's curriculum vitae and statement of acceptance of nomination. Biographical information for the following candidates will be enclosed with the ballots mailed to members in October.

Slate of Candidates

GENERAL ELECTION

President: Nina V. Fedoroff, U.S. Dept. of State; Alice P. Gast, Lehigh Univ.

Board of Directors: Roger N. Beachy, Donald Danforth Plant Sciences Ctr.; Stephen Mayo, California Institute of Technology; Susan Rosser, San Francisco State Univ.; Kenneth Prewitt, Columbia Univ.

Committee on Nominations: James McCarthy, Harvard Univ.; Pamela Bjorkman, California Institute of Technology; Diana H. Wall, NREL, Colorado State Univ.; Vinayak P. Dravid, Northwestern Univ.; Maxine Singer, Carnegie Institution for Science; Barbara Schaal, Washington Univ.; Tom Lovejoy, The Heinz Ctr.; Eric Barron, National Ctr. for Atmospheric Research

SECTION ELECTIONS

Agriculture, Food, and Renewable Resources

Chair Elect: Charles Arntzen, Arizona State Univ.; Eugene Nester, Univ. of Washington
Member-at-Large of the Section Committee: Jan Leach, Colorado State Univ.; Ken Moore, Iowa State Univ.

Electorate Nominating Committee: Ian Pepper, Univ. of Arizona; Shauna Somerville, Univ. of California, Berkeley; Jean Steiner, USDA-ARS Grazinglands Research Laboratory; Eleanore Wurtzel, Lehman College

Anthropology

Chair Elect: Cynthia Beall, Case Western Reserve Univ.; Dean Falk, Florida State Univ.
Member-at-Large of the Section Committee: Susan Antón, New York Univ.; Nina Jablonski, Pennsylvania State Univ.

Electorate Nominating Committee: Thomas Greiner, Univ. of Wisconsin, LaCrosse; Stephen Leigh, Univ. of Illinois, Urbana-Champaign; Jim McKenna, Univ. of Notre Dame; Kathleen O'Connor, Univ. of Washington
Council Delegate: Paul Leslie, Univ. of North Carolina, Chapel Hill; Pat Shipman, Pennsylvania State Univ.

Astronomy

Chair Elect: John Huchra, Harvard Univ.; Meg Urry, Yale Univ.

Member-at-Large of the Section Committee: Kevin Marvel, American Astronomical Society; Margaret Meixner, Space Telescope Science Institute
Electorate Nominating Committee: Giuseppina "Pepi" Fabbiano, Harvard Univ.; Jay Gallagher, Univ. of Wisconsin-Madison; Loren Acton, Montana State Univ.; Jay Pasachoff, Williams College
Council Delegate: Lori Allen, National Optical Astronomy Observatory; Tammy Smecker-Hane, Univ. of California, Irvine

Atmospheric and Hydrospheric Sciences

Chair Elect: Nominees to be announced
Member-at-Large of the Section Committee: Nominees to be announced
Electorate Nominating Committee: Nominees to be announced

Biological Sciences

Chair Elect: Kevin Struhl, Harvard Univ.; Mary Lou Guerinot, Dartmouth College
Member-at-Large of the Section Committee: Loren Rieseberg, Univ. of British Columbia; Peter Burgers, Washington Univ., St. Louis
Electorate Nominating Committee: Charles Aquadro, Cornell Univ.; Teresa Wang, Stanford Univ.; Jennifer Stone, Univ. of Massachusetts; Chris Amemiya, Benaroya Research Institute
Council Delegate: William Lucas, Univ. of California, Davis; Erin Irish, Univ. of Iowa; Susan Wessler, Univ. of Georgia; Rick Harrison, Cornell Univ.; Lynn Cooley, Yale Univ.; James S. Clegg, Univ. of California, Davis; Robb Krumlauf, Stowers Institute for Medical Research; James Marrs, Indiana Univ.; Peter Santi, Univ. of Minnesota; Eric Shelden, Washington State Univ.; Marc Feldman, Stanford Univ.; Anindya Dutta, Univ. of Virginia; David Gilbert, Florida State Univ.; Mosur Raghuraman, Washington State Univ.; Nancy Walworth, Univ. of Medicine and Dentistry of New Jersey; Bonnie Bartel, Rice Univ.; Ronald Hoy, Cornell Univ.; Victor D. Vacquier, Univ. of California, San Diego

Chemistry

Chair Elect: Nominees to be announced
Member-at-Large of the Section Committee: Nominees to be announced
Electorate Nominating Committee: Nominees to be announced

Dentistry and Oral Health Sciences

Chair Elect: Gary Armitage, Univ. of California, San Francisco; Nominee to be announced
Member-at-Large of the Section Committee: Kenneth Yamada, National Institutes of Health; Richard Lamont, Univ. of Florida
Electorate Nominating Committee: Dennis Mangan, Univ. of Southern California; Anne George, Univ. of Illinois, Chicago; Mina Mina, Univ. of Connecticut Health Ctr.; Mark Ling, Univ. of Chicago

Education

Chair Elect: Judith Ramaley, Winona State Univ.; Elizabeth Stage, Univ. of California, Berkeley
Member-at-Large of the Section Committee:

Sean Decatur, Oberlin College; Carlos Gutiérrez, California State Univ., Los Angeles
Electorate Nominating Committee: Rainer Glaser, Univ. of Missouri; Thomas Higgins, Harold Washington College; Patricia Mabrouk, Northeastern Univ.; Marilyn Suiter, National Science Foundation

Engineering

Chair Elect: H. Vincent Poor, Princeton Univ.; Ibrahim Hajj, American Univ. of Beirut
Member-at-Large of the Section Committee: Gary May, Georgia Institute of Technology; Braden Allenby, Arizona State Univ.
Electorate Nominating Committee: Rao Surampalli, U.S. Environmental Protection Agency; Dereje Agonafer, Univ. of Texas; Cynthia Bruckner-Lea, Pacific Northwest National Laboratory; Richard Alkire, Univ. of Illinois, Urbana-Champaign

General Interest in Science and Engineering

Chair Elect: Linda Trocki, Consultant; Judith E. Parker, Consultant
Member-at-Large of the Section Committee: Mary Mead Hammond, Carlson, Hammond & Paddock, LLC; Joan Horvath, Takeoff Technologies, LLC; Michael Isaacson, Univ. of California, Santa Cruz; James O'Brien, Tidewater Community College
Electorate Nominating Committee: Don Jordan, Univ. of South Carolina; Bassam Shakhshiri, Univ. of Wisconsin-Madison; Peter Farnham, American Society for Biochemistry and Molecular Biology; Deborah Illman, Univ. of Washington

Geology and Geography

Chair Elect: Patrick Bartlein, Univ. of Oregon; Ellen Mosley-Thompson, Ohio State Univ.
Member-at-Large of the Section Committee: Thomas Cronin, U.S. Geological Survey; Feng Sheng Hu, Univ. of Illinois, Urbana-Champaign
Electorate Nominating Committee: Susan Cutter, Univ. of South Carolina; George Malanson, Univ. of Iowa; Bruce Molnia, U.S. Geological Survey; Henry Pollack, Univ. of Michigan
Council Delegate: Thomas C. Johnson, Univ. of Minnesota; Douglas J. Sherman, Texas A&M Univ.

History and Philosophy of Science

Chair Elect: Jane Maienschein, Arizona State Univ.; Jeffrey L. Sturchio, Consultant
Member-at-Large of the Section Committee: Sally Gregory Kohlstedt, Univ. of Minnesota; Fae Korsmo, National Science Foundation
Electorate Nominating Committee: Ron Amundson, Univ. of Hawaii, Hilo; David Hounshell, Carnegie Mellon Univ.; Jay Malone, Univ. of Florida; Audra Wolfe, Chemical Heritage Foundation

Industrial Science and Technology

Chair Elect: Nominees to be announced
Member-at-Large of the Section Committee: Nominees to be announced

Electorate Nominating Committee: Nominees to be announced

Information, Computing, and Communication

Chair Elect: Nominees to be announced
Member-at-Large of the Section Committee: Nominees to be announced
Electorate Nominating Committee: Nominees to be announced

Linguistics and Language Science

Chair Elect: Barbara Abbott, Michigan State Univ.; Mark Liberman, Univ. of Pennsylvania
Member-at-Large of the Section Committee: Jennifer Cole, Univ. of Illinois, Urbana-Champaign; Andrea Levitt, Wellesley College
Electorate Nominating Committee: Nominees to be announced

Mathematics

Chair Elect: John Ewing, Math for America; Donald Saari, Univ. of California, Irvine
Member-at-Large of the Section Committee: Mary Ellen Bock, Purdue Univ.; De Witt Sumners, Florida State Univ.
Electorate Nominating Committee: Carl Cowen, Purdue Univ.; James Donaldson, Howard Univ.; Wade Ellis, West Valley College; Robert Megginson, Univ. of Michigan
Council Delegate: Philippe Tondeur, Univ. of Illinois, Urbana-Champaign; Michel Lapidus, Univ. of California, Riverside

Medical Sciences

Chair Elect: Edward Benz, Harvard Univ.; Charles M. Rice, Rockefeller Univ.
Member-at-Large of the Section Committee: Harriet Robinson, Emory Univ.; Peter Palese, Mt. Sinai School of Medicine
Electorate Nominating Committee: Dan Longo, NIA/NIH; Larry Corey, Univ. of Washington; Ruth Ruprecht, Dana Farber Cancer Institute; Lisa Guay-Woodford, Univ. of Alabama

Neuroscience

Chair Elect: Bernice Grafstein, Weill Cornell Medical College; Howard Eichenbaum, Boston Univ.
Member-at-Large of the Section Committee: Don Cleveland, Univ. of California, San Diego; Lynn Nadel, Univ. of Arizona
Electorate Nominating Committee: Charles Glabe, Univ. of California, Irvine; Michael E. Greenberg, Harvard Medical School; Earl Miller, Massachusetts Institute of Technology; Phyllis Wise, Univ. of Washington
Council Delegate: Amita Sehgal, Univ. of Pennsylvania; Diana Woodruff-Pak, Temple Univ.

Pharmaceutical Science

Chair Elect: Stuart Feldman, Touro College; John Slattery, Univ. of Washington
Member-at-Large of the Section Committee: Ah-Ng "Tony" Kong, Rutgers Univ.; Uday Kompella, Univ. of Colorado

Electorate Nominating Committee: Michael Mayersohn, Univ. of Arizona; Jashvant Unadkat, Univ. of Washington; Murali Ramanathan, SUNY, Buffalo; David Ross, Univ. of Colorado

Physics

Chair Elect: William Zajc, Columbia Univ.; Eric Heller, Harvard Univ.; J. Murray Gibson, Argonne National Laboratory
Member-at-Large of the Section Committee: Sekazi Mtingwa, Massachusetts Institute of Technology; Jolie Cizewski, Rutgers Univ.
Electorate Nominating Committee: S. Jim Allen, Univ. of California, Santa Barbara; B. Lee Roberts, Boston Univ.; Thomas Glasmacher, Michigan State Univ.; Katharine Gebbie, National Institute of Standards and Technology
Council Delegate: John Negele, Massachusetts Institute of Technology; Joe Hamilton, Vanderbilt Univ.; Robert Beichner, North Carolina State Univ.; Pierre Meystre, Univ. of Arizona; David Gross, Univ. of California, Santa Barbara

Psychology

Chair Elect: John Cacioppo, Univ. of Chicago; Nora Newcombe, Temple Univ.
Member-at-Large of the Section Committee: Jocelyne Bachevalier, Emory Univ.; Sue Carter, Univ. of Illinois, Chicago
Electorate Nominating Committee: Joe Martinez, Univ. of Texas; Janet Werker, Univ. of British Columbia; Sheri Berenbaum, Pennsylvania State Univ.; Hill Goldsmith, Univ. of Wisconsin

Social, Economic, and Political Sciences

Chair Elect: Kenneth Bollen, Univ. of North Carolina; Arthur Lupia, Univ. of Michigan
Member-at-Large of the Section Committee: Julia Lane, National Science Foundation; Walter Mebane, Univ. of Michigan
Electorate Nominating Committee: Edward Carmine, Indiana Univ.; David Collier, Univ. of California, Berkeley; Edward Lazear, Stanford Univ.; Nancy Lewis, East-West Ctr.

Societal Impacts of Science and Engineering

Chair Elect: Nominees to be announced
Member-at-Large of the Section Committee: Nominees to be announced
Electorate Nominating Committee: Nominees to be announced

Statistics

Chair Elect: Tom Louis, John Hopkins Univ.; Jessica Utts, Univ. of California, Irvine
Member-at-Large of the Section Committee: M. Elizabeth Halloran, Univ. of Washington; Stanley Lemeshow, Ohio State Univ.
Electorate Nominating Committee: Marie Davidian, North Carolina State Univ.; Nick Jewell, Univ. of California, Berkeley; Ed Korn, NCI/NIH; Javier Rojo, Rice Univ.

INTRODUCTION

Clearing the Air

IN 1895, THE GREAT SWEDISH CHEMIST SVANTE ARRHENIUS USED BASIC PHYSICAL concepts, already well understood at the time, to describe how variations in trace gases in the atmosphere—particularly CO_2 —should influence the heat budget of Earth. By establishing the connection between higher concentrations of atmospheric CO_2 and higher atmospheric temperatures, Arrhenius laid the foundation of modern climate-change research, which is dominated by the understanding that the steadily increasing atmospheric CO_2 concentration, caused mostly by fossil-fuel burning, is the main reason why the world's climate is warming so much and so rapidly. If too much CO_2 in the air is the cause of our climate dilemma, then it seems obvious that we should slow down, stop, or even reverse its current rise to mitigate the risk of unwanted climate changes. Carbon capture and sequestration, or storage, (CCS) is rapidly becoming a key element in our nascent efforts to minimize the amount of CO_2 we emit and perhaps even to regulate the amount of CO_2 in the atmosphere.

This special issue aims to elucidate some of the main approaches to CCS and how they might be accomplished. In the Review, Haszeldine (p. 1647) surveys efforts around the world to capture and store CO_2 emitted by power plants, discussing both the technological challenges of carbon capture, transport, and storage and the political hurdles that remain to be overcome. Four Perspectives then highlight specific approaches to both CO_2 capture and CO_2 sequestration. Rochelle (p. 1652) discusses how CO_2 can be removed from the flue gas of power plants by the well-established technique of amine scrubbing, an especially important activity given the current reliance on coal. Keith (p. 1654) presents ideas about removing CO_2 directly from ambient air, one of the few approaches that offer the possibility of reducing the concentration of CO_2 in the atmosphere on a time scale of decades. Orr (p. 1656) discusses the current strategy of choice for sequestering captured CO_2 permanently: the storage of CO_2 in onshore geologic formations. Finally, Schrag (p. 1658) argues for another promising but rarely discussed way to sequester CO_2 : through storage in offshore sediments.

In News, Dennis Normile (p. 1642) offers a guide to the carbon cycle, a quick introduction to carbon sources and sinks, and a look back at how atmospheric CO_2 has varied over the past 500 million years or so. Robert Service (p. 1644) provides a map of major CCS projects around the world, showing mainly projects already in progress or under construction. Finally, Josh Fenn (p. 1646) profiles two CCS projects in China which, though at early stages, are potentially important in a country with such a surging demand for fossil fuels.

The prospects of CCS are uncertain, but its promise is great. If this special issue has any single most important message, it is that there are abundant reasons to hope that CCS can be implemented effectively.

—H. JESSE SMITH, JULIA FAHRENKAMP-UPPENBRINK, ROBERT COONTZ

Carbon Capture and Sequestration

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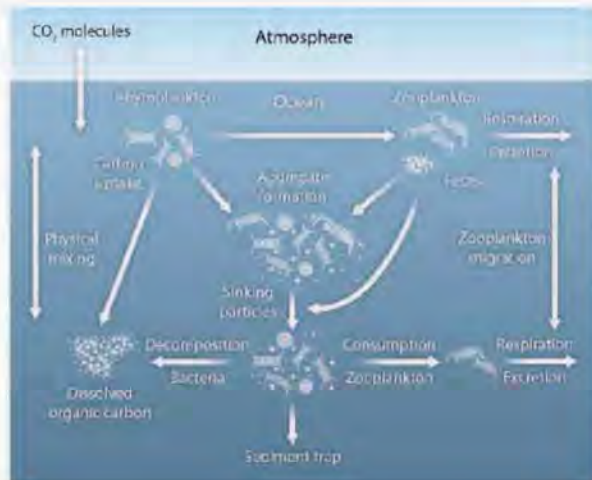
Round and Round

A Guide to the Carbon Cycle

Carbon continuously cycles through living creatures, the atmosphere, the oceans, and Earth itself in one of nature's more amazing balancing acts. The main building block of life, carbon is fixed into terrestrial and marine other organisms tissue through photosynthesis. Animals eat other organisms and burn carbohydrates for energy, releasing carbon dioxide (CO_2) through respiration and through decay after death. For much longer than humans have walked the earth, carbon generation has roughly equaled carbon consumption. But humankind has tipped the scales, adding CO_2 to the atmosphere by burning fossil fuels—the products of eons of accumulated plant matter transformed into coal and oil by geologic processes.

Illustration: C. Bickel/*Science*; graphics and layout: N. Kevitiyagala/*Science*

—DENNIS NORMILE

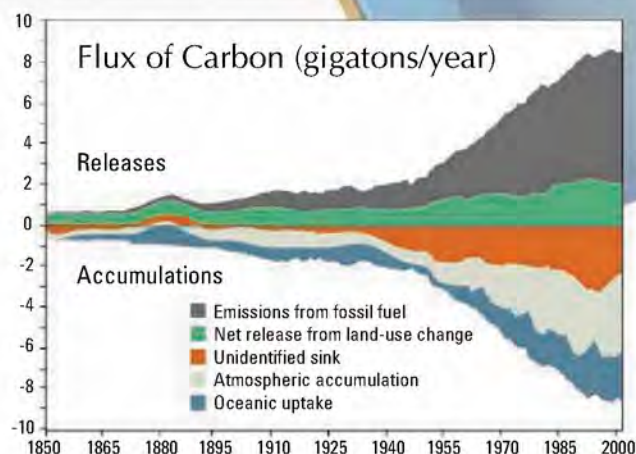


Into the Deep

Cool oceanic waters absorb CO_2 , and cold currents at high latitudes carry dissolved carbon to the deep ocean; upwelling in the tropics brings much of it back up, and warm waters pass it back into the atmosphere. Meanwhile, tiny oceanic plants called phytoplankton absorb CO_2 through photosynthesis, forming the first link in the marine food chain. Sinking fecal matter and decaying organisms take small amounts of carbon to the sea floor. This all results in a small net uptake of carbon by burial in ocean sediments.

Dark Mysteries

Humans are now pumping more than 7 gigatons* of CO_2 into the atmosphere each year, but scientists figure only about 50% remains there. Where does the rest of it go? Possibilities include greater-than-expected uptake by northern forests, the oceans, and desert soils. Solving the mystery is more difficult because of uncertainties about how much carbon is going where. Estimates of the amount of carbon emitted by clearing forests could be off by as much as 100%, according to the U.S. Climate Change Science Program, though other flux estimates are believed to be closer to the mark.



*All units are metric. (Source: Woods Hole Research Center)



Ins and Outs

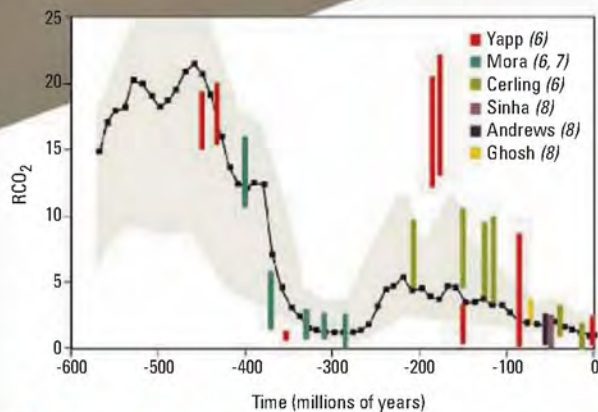
Carbon sinks:

Vegetation net production: 57 gigatons/year
 Ocean absorption: 92.2 gigatons/year
 Land sinks: 2.3 gigatons/year

Carbon sources:

Vegetation respiration: 55.5 gigatons/year
 Ocean outgassing: 90.5 gigatons/year
Fossil fuel and cement emissions: 6.4 gigatons/year
 Changes in land use: 1.2 gigatons/year

(Source: *The First State of the Carbon Cycle Report*, U.S. Climate Change Science Program)



Ups and Downs

The amount of carbon in the atmosphere has varied widely over geologic time owing to the effects of ice ages, volcanism, asteroid impacts, and the spread and retreat of vegetation. About 500 million years ago, atmospheric CO₂ density may have been 20 times as high as it is today. Atmospheric CO₂ for most of the past 10,000 years hovered around 280 parts per million, but increasing use of fossil fuels since the Industrial Revolution has pushed it to its current level of about 385 ppm.

(Source: University of California, San Diego)

Carbon Sequestration

To slow the atmospheric buildup of CO₂, a report from the U.S. National Research Council recently called for building a suite of 15 to 20 power plants with carbon capture and storage (CCS) before 2020. "The urgency of getting started on these demonstrations to clarify future deployment options cannot be overstated," the report said. Today, a few such projects are under development. Most aim either to bury CO₂ separated from natural gas reservoirs or to pump it into oil reservoirs to push out more oil. This map shows some of the major CCS projects around the world.

Adapted from the Scottish Centre for Carbon Storage, University of Edinburgh. Sources: U.S. DOE, (Individual projects) MIT Carbon Capture and Sequestration Technologies, International Energy Agency, Cooperative Research Centre for Greenhouse Gas Technologies (CRCCO2), (Graphics and layout: N. Kevitiyagala/Science)



1 Weyburn-Midale Project

SASKATCHEWAN, CANADA

Size: 1 million metric tons per year (Mt/yr)
Start Date: 2000

CO₂ from a synfuels plant in North Dakota in the United States is piped 330 km to Weyburn, where it is pumped into an active oil well to enhance the amount of recovered oil.

2 Southwest Regional Partnership

PRICE, UTAH, USA

Size: Up to 900,000 metric tons CO₂ over 4 years
Start Date: 2008

CO₂ will be injected into deep underground saltwater formations that are primary targets for commercial-scale CO₂ disposal from future coal-fired power plants planned for the area.

3 Schwarze Pumpe

SOUTHEAST OF BERLIN, GERMANY

Size: 100,000 metric tons of CO₂ over 3 years
Start Date: 2009

CO₂ from a lignite- and coal-burning pilot plant will be captured, liquefied, and injected underground.

4 K12-B CO₂ Injection Project

NORTH SEA, NETHERLANDS

Size: 200,000 metric tons/yr
Start Date: 2004

The K12-B site has produced natural gas since 1987. CO₂ from the field is now separated from the natural gas and reinjected into the same reservoir from which it came.

5 Sleipner West

NORTH SEA, NORWAY

Size: 1 Mt/yr
Start Date: 1996

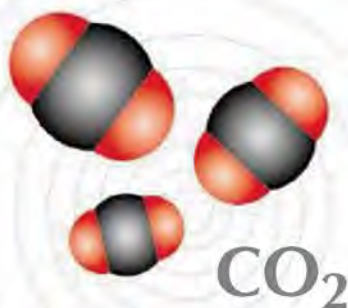
Natural gas pumped from this North Sea gas rig is stripped of CO₂, which is then reinjected into a deep geological layer below the Sleipner platform.

6 Snøhvit

BARENTS SEA, NORWAY

Size: 700,000 metric tons/yr
Start Date: 2008

This offshore gas field produces liquefied natural gas. CO₂ is separated from the gas and reinjected 2600 meters below the sea floor.





Project Stages

- Planning
- In process
- Completed

7 Recopol

KANIOW, POLAND
Size: 760 metric tons of CO₂
Start Date: 2004

The first project of its kind in Europe. CO₂ was stored initially as a liquid, then heated and injected into coal seams about 1100 meters underground. Injection ended in 2005; site monitoring continues.

8 In Salah

IN SALAH, ALGERIA
Size: 1.2 Mt/yr
Start Date: 2004

CO₂ from this natural gas field is compressed and reinjected into a water-filled deposit 1800 meters below the ground.

9 GreenGen

TIANJIN, CHINA
Size: 1 Mt/yr
Start Date: 2016

CO₂ from gasified coal will be recovered before combustion and probably used in oil recovery. (See page 1646.)

10 Erdos

ERDOS, INNER MONGOLIA, CHINA
Size: up to 3.6 Mt/yr
Start Date: late 2009

An innovative coal-to-liquid fuel plant will capture CO₂ for use in oil recovery. (See page 1646.)

11 Otway Basin

SOUTHWEST VICTORIA, AUSTRALIA
Size: 100,000 metric tons CO₂ over 1 to 2 years
Start Date: late 2008

Australia's first CO₂ deep geological sequestration demonstration project. CO₂ from a natural gas well is separated, compressed, and injected into a depleted gas reservoir some 2050 meters underground.

12 Gorgon

BARROW ISLAND, AUSTRALIA
Size: 3.3 Mt/yr
Start Date: 2009

One of the world's biggest CO₂ sequestration experiments. CO₂ from natural gas fields will be separated and injected into a saltwater reservoir 2300 meters below Barrow Island in Australia.



China Grapples With A Burning Question

Two new projects mark the coal-hungry country's first major steps toward trapping carbon emissions

BEIJING—In the coming weeks, on the plains of Inner Mongolia, China plans to launch its first large-scale effort to capture and store carbon emissions. A new coal-to-liquid plant in Erdos will burn coal to make, at the outset, a little over 1 million metric tons per year of diesel and other petrochemicals. Operated by China's biggest coal producer, Shenhua Group, the plant will generate as a byproduct about 3.6 million tons of carbon dioxide (CO₂) a year. In an effort to make carbon capture pay, much of the gas will be sequestered in nearby oil reservoirs, where pressure from the CO₂ will force hard-to-get oil to the surface.

Shenhua's plant is one of two pivotal carbon capture and storage efforts in China. The other is GreenGen, an integrated gasification combined cycle (IGCC) plant that the Chinese government approved last June for construction in Tianjin. Instead of pulverizing coal as a conventional power plant does, IGCC plants turn it into gas, which allows for easy separation of CO₂ from combustible gases—and far easier CO₂ capture. If successful, GreenGen could redefine how power is generated from coal in China, says Richard Morse of the Program on Energy and Sustainable Development at Stanford University in Palo Alto, California. "You could make a very strong case that it's the leading carbon-capture project for coal-fired power in the world," he says.

As China's economy booms, the need for carbon capture and storage is becoming increasingly urgent. Electricity consumption has shot up more than 50% in the past 5 years, and the country uses nearly 200 million more tons of oil per year than it did 10 years ago. For the next half-century or so, experts say, China will likely have to rely on coal to meet most of its energy needs. Carbon capture and storage technologies may require steep investments, but they are a must to stem environmental deterioration, says Simon Hayles, a bioenergy and carbon-capture project manager at the energy and environment consultancy AEA in Oxford, U.K.

A perennial question in China as elsewhere is how to offset the costs of carbon capture. One approach is to make use of CO₂ above ground. Last year, Huaneng Group, China's biggest electricity provider, and Australia's Commonwealth Scientific and Industrial Research Organisation commissioned a coal-burning power plant in suburban Beijing capable of capturing 3000 tons of CO₂ per year. The gas is sold to local soft-drink manufacturers to put the fizz in carbonated beverages. Huaneng plans to scale up with its Shidongkou No. 2 Power Plant carbon capture project, a suite of carbon-capture facilities to be added to an existing coal plant in Shanghai. Expected to be operational by the end of 2009, the project will capture roughly 100,000 tons of CO₂ per

All gassed up. GreenGen will skim off CO₂ before gasified coal is burned.

year and sell the gas to soda companies and other local industries.

But such industries can put to use only a tiny fraction of CO₂ emissions. That's why China is turning to enhanced oil recovery for carbon capture, says Deborah Seligsohn, principal adviser of the World Resources Institute's Beijing office. PetroChina has in the past used water and various polymers to recover oil in the country's northeast, she says. The Erdos plant shifts the emphasis to carbon sequestration. It will eliminate an intermediate gas-producing step used by other coal-to-liquid plants and use a relatively pure stream of CO₂ for oil recovery.

Experts are even more enthusiastic about Tianjin's GreenGen project. The plant will skim off CO₂ from gasified coal before it is burned, a huge increase in efficiency compared with older plants that attempt to sop up CO₂ from emissions after combustion. In the long run, IGCC could be an economic boon—and China has a head start on the competition, says Morse. "IGCC is likely to be the most viable path forward for carbon capture on coal plants in China," he says.

By 2011, GreenGen is expected to be running at a capacity of 250 megawatts of electricity, says Liu Yu, a GreenGen research engineer. An additional 450-megawatt facility able to capture more than 1 million tons of CO₂ emissions per year will be completed by 2016, says Yu. The likeliest use of the CO₂, experts say, is enhanced oil recovery.

Fortunately, China has plenty of places to sock away CO₂. According to a preliminary report by geologist Li Xiao Chun of the Chinese Academy of Sciences Institute of Rock and Soil Mechanics in Wuhan, China has some 46 natural gas and oil reservoirs, 68 coal beds, and 24 saline aquifers that could be used to sequester CO₂. That equates to a CO₂ storage capacity of some 3.2 trillion tons, Li says. If it's economically feasible to store carbon even in only 10% of these formations, he says, China could tuck away a century's worth of emissions before running out of space.

Major sequestration efforts in China—such as funneling tens of millions of tons of CO₂ into reservoirs or aquifers—are years away. But with key carbon capture and storage projects finally getting off the ground, China could soon be breathing at least a little bit easier.

—JOSH FENN

Josh Fenn is a writer in Beijing.

CREDIT: GREENGEN



REVIEW

Carbon Capture and Storage: How Green Can Black Be?

R. Stuart Haszeldine

The capture of carbon dioxide at the point of emission from coal- or gas-burning power plants is an attractive route to reducing carbon dioxide emissions into the atmosphere. To commercialize carbon capture, as well as transport of liquified carbon dioxide and its storage in exploited oil fields or saline formations, many technological, commercial, and political hurdles remain to be overcome. Urgent action is required if carbon capture and storage is to play a large role in limiting climate change.

Carbon dioxide emissions from fossil fuel combustion are a major contributor to climate change (1). The current low price of fossil fuel energy is partly subsidized by unpriced CO₂ emissions, exploiting the degradation of natural atmosphere and ocean. Even if the debate on climate change is over, the actions to limit CO₂ emissions have barely started.

One step toward reducing CO₂ emissions is to capture the CO₂ generated during combustion and store it in a suitable place. This process of carbon capture and storage (CCS) has the potential to reduce future world emissions from energy by 20% (2). CCS is already operating in trials, with 3 megatons of CO₂ (Mt CO₂) per year from power plants or natural gas cleanup being captured and stored. CCS technologies are now in a scale-up period. Worldwide, large demonstrations are planned on 36 power plants. However, there is a lamentable lack of financial commitment to real construction. If design and construction of these demonstration plants does not start now, they will not operate by 2014, and learning from these to provide commercial credibility will drift beyond 2020. The worldwide construction of many tens to hundreds of large CCS plants—necessary for a substantial impact on climate mitigation—will then be delayed beyond the deadline set by climate change predictions.

Will CCS actually deliver material reductions of CO₂ before 2030? Or is it instead a set of over-ambitious promises that act as an excuse for power generators to pollute with black coal and “clean” gas under a pretext of green development, locking the world into decades of high CO₂ emissions (3)? Here, I analyze the technical challenges associated with capture, transport, and storage of CO₂ and then look at what needs to be done for a viable CCS industry to be created between 2020 and 2030.

The Purpose of CCS

There is a broad political consensus that the global temperature rise should be limited to 2°C, compared with preindustrial temperatures. However,

such declarations lack urgency, targets, or specified time scales. The scientific analysis has swung to define CO₂ limits not as a tonnage released per year, but as the total mass of fossil carbon released during this geologically short industrial time span (4). CO₂ emissions must therefore start to fall from 2020 onward. CCS is unavoidable if fossil fuels continue to be burned at more than 10% of the present rate. It is surprising, then, that so few CCS projects are underway.

Fossil fuel combustion supplies more than 85% of energy for industrial activities (5) and is thus the main greenhouse gas contributor. Coal is on a path to supply 28% of global energy by 2030, as part of a 57% increase in CO₂ emissions (5). CCS is a direct emissions mitigation option, usually considered as an interim system to enable a 50-year transition away from fossil fuels. Although current CCS technologies are only at the pilot stage, the

scale of the main ambition is massive: to fit all coal and gas power plants with CCS by 2050 and reduce world CO₂ emissions from energy by 20% (2). Accordingly, CCS will incur incremental costs. For example, in the U.K., CCS may cost each household an extra 10% per year for electricity. That may seem expensive, but if CCS is developed now as part of a portfolio of global climate protection, the costs of CO₂ abatement required in 2050 are predicted to reduce from \$500 to \$50 per ton (2).

CCS strips out, purifies, and concentrates CO₂ emissions from fossil fuel combustion at large single sources such as power plants (Fig. 1). Three methods of CO₂ capture are currently being investigated (1). Postcombustion capture separates the CO₂ with the use of chemical solvents, precombustion capture chemically strips off the carbon, leaving hydrogen to burn, and oxyfuel combustion burns coal or gas in denitrified air to yield only CO₂ and water. After leaving the power plant, the captured CO₂ is pressurized to 70 bar, forming a liquid that can be transported to a storage site, where the fluid is injected into rock pores deeper than 800 m below the surface (6, 7). Good choices of storage sites will retain CO₂ without appreciable seepage for tens of thousands of years. Monitoring will be required for decades into the future, combined with techniques to remediate deficient storage. In principle, CCS can be applied not only to power plants but also to large industrial sites, such as refineries, steel making, fertilizers, ethanol fermentation, and cement manufacture (1). However, these applications are proving to be quite slow to develop on a global level. The

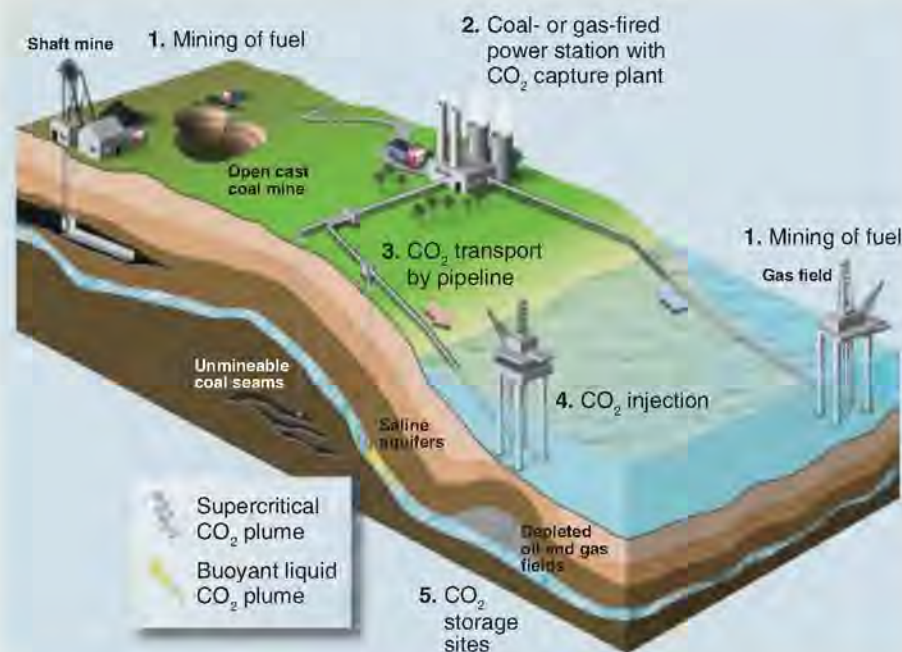


Fig. 1. Diagrammatic representation of the life-cycle chain of fossil fuel use. CO₂ separation and capture at power plants enables storage of CO₂ in porous rocks deep below ground.

Carbon Capture and Sequestration

present CCS discussion focuses on power plants fired by fossil fuels (coal, gas, and oil) and sometimes co-fired with biomass.

Technical Challenges

Carbon capture. Separation of CO₂ is the step that consumes the most energy and results in the highest cost. Historical examples of CO₂ separation, if scaled-up, could consume 25 to 40% of the fuel energy of a power plant and be responsible for 70% or more of the additional costs in CCS (8). The developments currently under way should result in tangible improvements toward a 10 to 20% energy penalty. For commercialization, it is normal practice to construct progressively larger equipment from pilot to demonstration plants (Fig. 2). This practice enables learning to increase reliability and reduce cost. The three capture methods are currently indistinguishable in cost and efficiency.

In postcombustion capture, a solvent absorbs CO₂ from flue gas and is regenerated by heating for several hours in recovery columns at 150°C. In this case, the challenges are to scale up by a factor of 50 from the largest current operation while protecting the solvent from degradation by flue-gas impurities. Modified and new amine solvents are being tested in the European Union (EU) CO₂CASTOR and SOLVIT projects, which aim to halve energy penalties. Pilot plants up to 5 MW in the U.S. are investigating new ammonia-based processes, and in 2009, the U.S. Department of Energy (DOE) awarded \$100 million (9) to support a 1 Mt per year demonstration. The U.K. will fund a 400-MW commercial retrofit on coal plant, working in 2014 (10).

Postcombustion amine capture has some major disadvantages: The equipment will be very large, comparable with the footprint size of a coal-fired power plant, large volumes of solvent are needed, heating to regenerate the solvent can produce toxic byproducts, emissions of solvents from recovery columns need to be scrubbed and eliminated, consumption of water needs to be reduced, and expired solvent needs to be disposed. However, postcombustion capture also has distinct advantages. It can be applied to already constructed plants, operated with the plant to capture CO₂, or disconnected to provide maximum power output at times of peak electricity price. Furthermore, components in the non-integrated equipment can be replaced, developed, and upgraded without fundamental impact on the power plant. Future developments may increase efficiency through closer integration of capture with the host plant, and novel membranes or microporous solids may help to separate N₂ and other minor gases from CO₂. Cryogenic capture has also been proposed at an experimental scale (11), including

SO_x, NO_x, and Hg elimination, with the cost per ton of CO₂ capture reduced by 40%.

Oxyfuel combustion has not previously been developed for use in large-scale power plants. This process separates oxygen from air with the use of established cryogenic methods and then burns the coal or gas fuel in a mixture of that oxygen, combined with recycled flue gas to cool the combustion. Burners for oxyfuel have been demonstrated at 1-MW scale, and the world's largest experiments are developing 40-MW burners, intended to be commercially available from 2015 (12). Two pilot plants are in operation: Schwarze Pumpe in Germany has burned lignite or bituminous coal since 2008, and Lacq in southwest France has burned gas since 2009. Scale-

cycle power plant with CCS, projected to be operating in 2011 (13). The U.S. FutureGen project will develop a 275-MW precombustion plant with CCS in Illinois; this project was reactivated in 2009, with \$1.7 billion from the DOE and commercial partners (14). Several commercial developments seem likely to operate before 2015 (15) in the U.S. (9, 16); Alberta, Canada; Queensland, Australia; U.K., and Abu Dhabi, United Arab Emirates (16).

Advantages of precombustion capture are that multiple fuels can be used and multiple products produced, from electricity to hydrogen. The process is technically elegant, with efficiency gains from the integration. This could become a technology of choice for new-build plants sup-

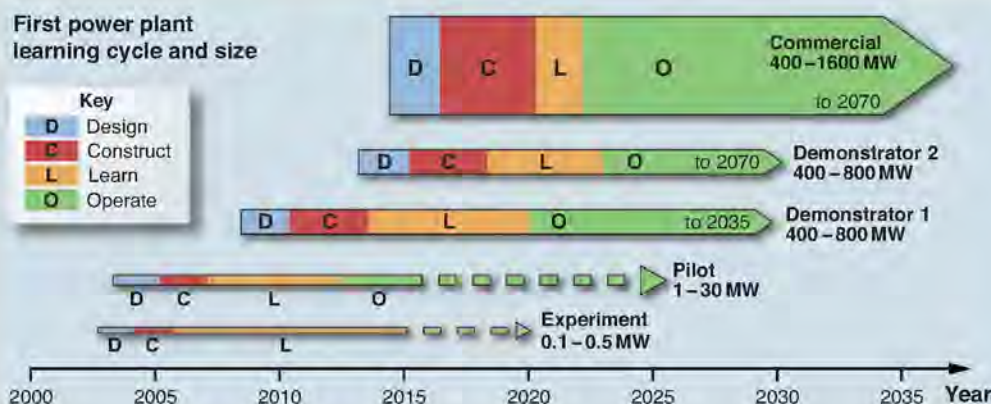


Fig. 2. Time chart showing how a CCS power plant can be increased to reliable and cost-effective commercial size by 2020, by means of progressively larger experimental equipment. Rapid information flow on the vertical axis is important from learning to subsequent design. This depends on industrialized nations providing financial support for CCS plant during the pilot and demonstration phases. Tens of large CCS demonstrators need to be built worldwide from 2009. Incentive systems (for instance, premium payments for decarbonized electricity) are needed to enable introduction, operation, and establishment from 2014 to 2020.

up to a power plant involves the use of multiple burners and air separation trains.

Attractions of oxyfuel combustion are the much easier separation of CO₂, with no solvent, smaller physical size, and the potential to retrofit on existing plants (if the boilers are also reconstructed). Drawbacks are the very low SO_x required on leaving burners, as well as the higher-temperature materials that are also required. Future developments could improve high-temperature operation and reduce the energy costs of O₂ separation from air.

Precombustion capture involves constructing plants to gasify coal and chemically shift syngas or methane to hydrogen. Using this process, CO₂ capture is already proven to work at the megaton-per-year scale but has not been fitted to an operational power plant. The challenge here lies less in the basic technology and more in the reliability of all components for total continuous integration. In China, the GreenGen 250-MW project southeast of Beijing will potentially be the world's first Integrated Gasification Combined

plying solely baseload electricity. Disadvantages are high construction costs and decreased short-term flexibility. Future gains may come from the development of high-temperature membranes that allow syngas to be catalytically reformed into CO₂ at the same time as hydrogen is separated.

For all capture technologies, the road to rapid commercial deployment is much less certain. At least two learning cycles are needed (Fig. 2) to demonstrate operation and enable commercial guarantees for construction, to begin globally in 2020 (17). This is a technically possible but politically optimistic pathway. With three major technologies, replication of each will be slower than if one type of capture becomes dominant. Consequently, promises to green the dirtiest fuel may be delayed.

Transport. CO₂ has been transported in pipes since the 1970s in the U.S. and Canada, where more than 3000 km of operational CO₂ pipes exist, transporting 30 Mt CO₂ per year. There are no known show-stoppers for pipeline developers, but there are many aspects for which more tech-



nical detail and safety criteria for populated areas would be helpful.

If the CO₂ is dry (less than 10 parts per million of water), conventional carbon steel can be used, greatly reducing the cost and also removing the risk of hydrate crystallization. CO₂ feed-in will contain impurities, depending on the plant type and capture system. These impurities could be N₂, O₂, H₂S, and/or SO₃. This multicomponent mixture increases the operational pressure needed to avoid dew-point condensation into liquids from ~73 bar in pure CO₂ to ~90 bar in CO₂ with impurities. To avoid costs of overcompression, a pipeline purity standard will be needed. If continental-scale transport is envisaged (e.g., across the EU or U.S.), standards need to be set early.

CO₂ can be gathered from multiple power plants (Fig. 3), transported through a shared system to the coast, compressed up to 150 bar, and trans-

mitted to offshore nodes. From those, CO₂ can be redistributed to individual storage sites (aquifers, oil fields, or gas fields) at the appropriate pressure and rate (18, 19). Targets for CCS tonnages are needed to predict the size of pipe needed. Commercial innovation is required if pipe operators function as the contractual links between operators of CO₂ capture (where risks are low and return on investment is also low) and subsurface storage operators (where risks are high, but return on investment is potentially very high). Diverse commercial solutions have been proposed. Norway will form a state company, but the U.K. expects a commercial pipe operation.

Injection and geological storage. To have an impact on worldwide emissions of fossil fuel-derived CO₂, extremely large volumes of geological storage are needed in the right places and at the right times. Injection of CO₂ for storage into microscopic pore space of sedimentary rocks is

based on industrial experience of injection into hydrocarbon fields from enhanced oil recovery (EOR) activities since the 1970s. Commercial injection has been undertaken into saline formations at 1 Mt/year or more at Utsira and Snøhvit, Norway and In Salah, Algeria. Natural sites have stored CO₂ for tens of millions of years (20, 21). However, efforts to scale-up injection face a fundamental problem: The subsurface contains no empty space. Any injection of CO₂ into a depleted hydrocarbon field or a saline formation has to displace or compress the existing pore fluid by raising the pressure.

In an oil or gas field, the pressure can be securely raised to return to the pressure at the date of discovery. The topographic hydrocarbon trap localizes the CO₂ so that pre-CCS boreholes can be monitored for leakage decades after injection. Yet even so, there are pitfalls. CO₂ is not an ideal gas and has a large Joule-Thomson effect (22, 23). If CO₂ is injected at 140 bar into a reservoir, it will expand into depressurized gas reservoirs at 10 to 30 bar and then cool (24). The resulting risks include hydrate ice crystallization in reservoir pores, blocking injection around the borehole, and thermal fracturing of cement seals, inducing CO₂ leakage. Simulation suggests that heating injected CO₂ to 75°C may overcome the problem (25), but practical demonstrations are needed.

Injection into depleted oil fields can also be difficult because in many fields, water injected to undertake secondary oil recovery partially fills the space formerly occupied by oil. To take advantage of the oil field containment structure, it may be necessary to empty it by producing extra oil. In this EOR process, injection of fluid CO₂ reduces oil viscosity and pushes oil toward production boreholes (26). CO₂-EOR is established and viable onshore in several countries. The American Recovery and Re-investment Bill 2009 provides \$3.4 billion for CCS demonstration and reduced-tax incentives for CO₂-EOR already existing in several U.S. states. An assessment of EOR in the U.S. optimistically calculated that 88 billion barrels of oil could be recovered from 330 billion remaining, even though in 2004, CO₂-EOR production was only 75 million barrels per year (27). Although CO₂-EOR is plausible onshore, it has not been shown to be viable offshore. Since 2000, several fields evaluated in the North Sea by Shell, British Petroleum, Norsk-Hydro, and Statoil

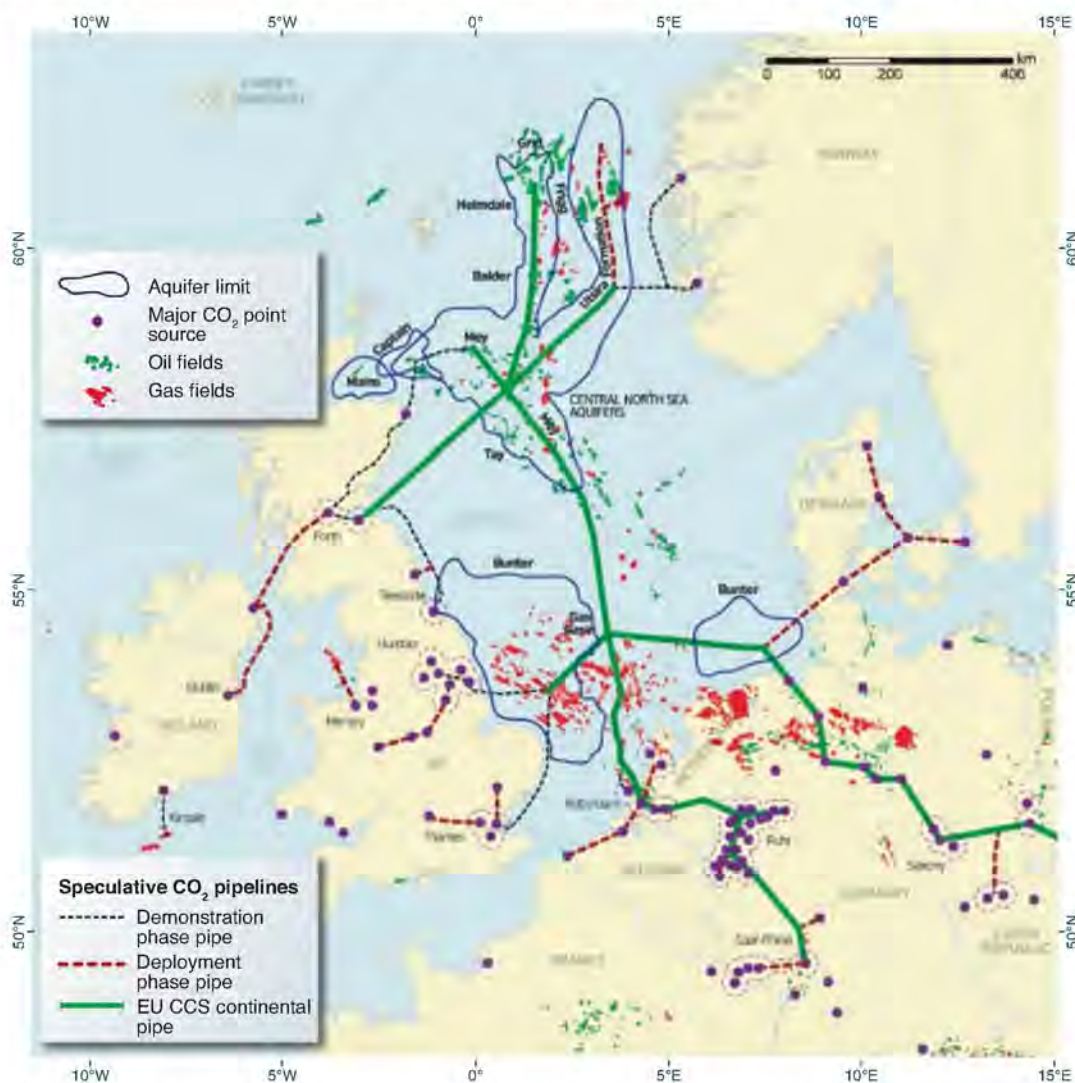


Fig. 3. Map of northwest Europe, showing sites of emissions, saline formations, gas fields, and oil fields. CO₂ can be collected from clusters of large power plants and transported to storage. This transport scenario visualizes pipelines built to offshore hubs accessing large-scale storage beneath the North Sea. Such sites can be evaluated with the use of legacy hydrocarbon data and may prove to be more reliable to develop and monitor than onshore storage. [Basemap of hydrocarbon fields supplied by M. Ricketts, Wood Mackenzie]

Carbon Capture and Sequestration

have failed commercial hurdles as a result of unreliable CO₂ supply, very large refit costs of offshore platforms, long times until positive cash flow, and much cheaper methods of additional oil production by drilling targeted and deviated boreholes. A sustained oil price of at least \$100 per barrel plus guaranteed availability of CO₂ are requirements for North Sea EOR viability (18).

Saline formations (aquifers) are not restricted to hydrocarbon provinces and have been calculated to provide, by far, the greatest storage volumes worldwide, equivalent to hundreds of years of present day power plant emissions (1). However, these calculations are probably too optimistic (7), because they do not consider that static storage volumes will be reduced as a result of inefficient dynamic sweep of CO₂ through a reservoir. Increased fluid pressure also imposes a limit on CO₂ injection volumes, because pre-existing faults and fractures can be re-opened to form leakage conduits. Additionally, CO₂ in unconfined formations (without structure traps) may migrate tens of kilometers during a 30-year injection period, making prediction and monitoring more expensive. For example, the 25,000 km² North Sea Utsira formation can potentially store 50 gigatons of CO₂, with a static efficiency using 9% of pore space. Yet dynamic injection today fills only 0.2% of the pore space. Modeling of dynamic injection shows that large-scale

extraction of deep water and disposal into the ocean is required if the larger volumes are to be achieved (28). For a smaller (4000 km²) North Sea aquifer, a static calculation gave a capacity of 2% of porosity, but this amount dropped to 0.56% of porosity when dynamic reservoir heterogeneity was added, and it dropped further to 0.2% when a pressure limit was also applied (18).

Worldwide, the original static estimates of storage capacity are now being substantially downgraded to many decades rather than hundreds of years of emissions. Only after dynamic demonstrations in aquifers will true capacity values become apparent, to determine if CCS can provide a niche or a major mitigation of CO₂.

CCS Aspirations Versus Real Projects

Although no fully functioning CCS power plant has yet been built, more than 20 experiments and pilots (Fig. 2) are currently operating (15). Some of these pilots capture 0.001% of CO₂ emitted from a full-size power plant, and others capture all emissions from 1/10th-scale plants. Separate injections of CO₂ test aquifer or oil field storage. The ambition (29, 30) is that multiple full-size demonstration plants (> 400 MW) will operate from 2014 (Fig. 4). A minimum of two cycles of demonstration plants are needed (17) to improve subsequent constructions before attempting to build commercial plants by the "climate deadline" of 2020. The overlap of learn-

ing into the next phase of construction will disappear if the first plants are not operational by 2015 (Fig. 2); thus, work on their design needs to start in 2009. Delay does not negate the utility of CCS, but it means that reductions of CO₂ emissions do not occur until after greenhouse gas forcing of climate progresses beyond the point of predictability (31). For the green aspirations of CCS to become real by 2020, funding and immediate building of real projects is needed.

Create Business, Make Learning Rapid

Expecting the translation of all 36 announced demonstrations (Fig. 4) into operation is overly optimistic for three reasons. First, the largest blockage is not technological, but rather the lack of a market to provide revenue that justifies large investment. Each demonstration coal plant requires a system for price support for many years to recover the \$1.5 billion extra capital and operational cost of generating decarbonized electricity. The pricing provided by the current carbon market is far too low and erratic. Price support systems are needed to introduce CCS, just as price support is given to introduce renewable energies. But this critical commercial help has been announced only for very few CCS projects. Paradoxically, in markets where renewables have price support to encourage deployment, cost compilations show that CCS will be a cheaper option to deploy (32).

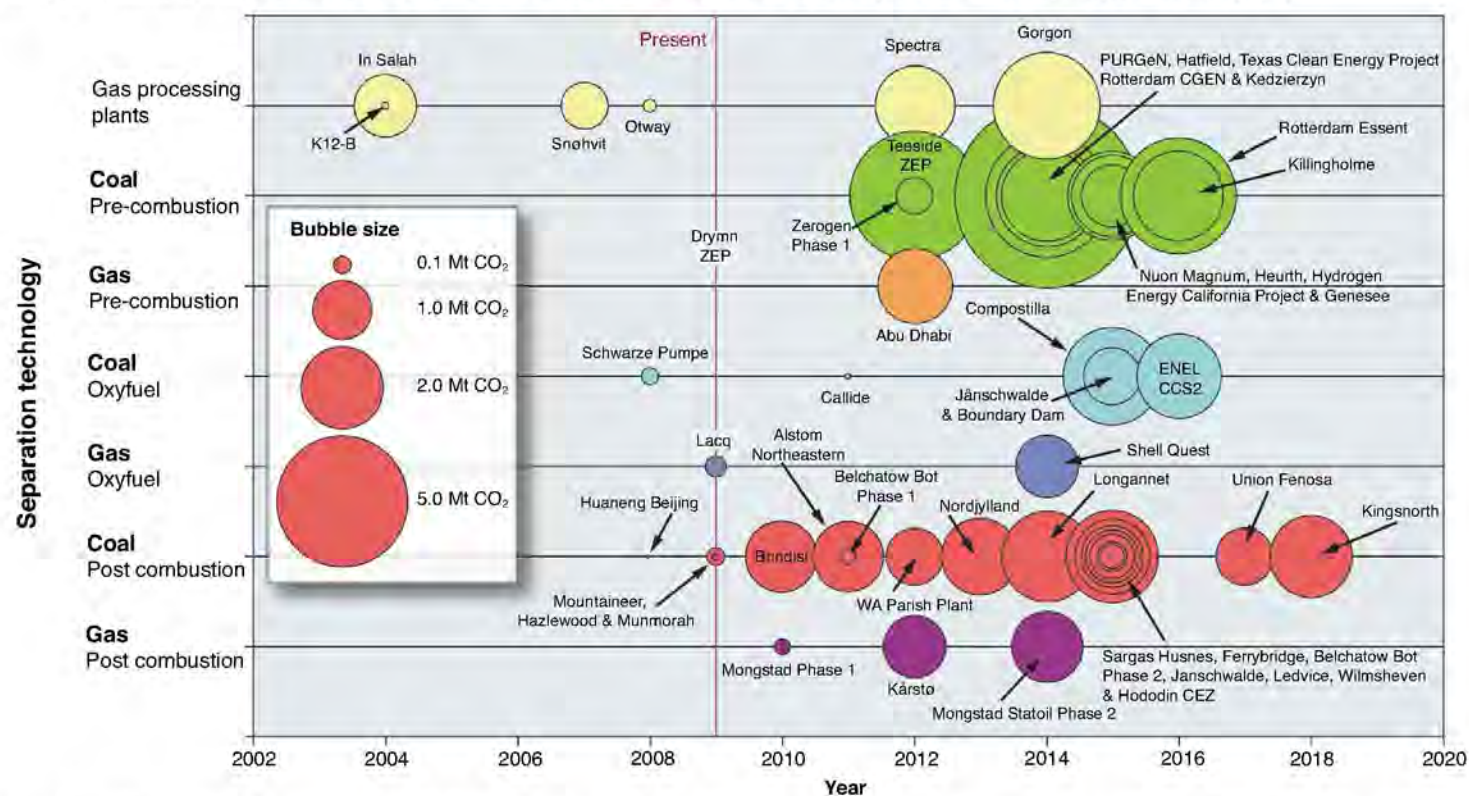


Fig. 4. Chart of large CCS demonstration projects planned worldwide, plotting calendar year against capture type and fuel. Coal and postcombustion power plants dominate. There is typically a 5-year lead time on design and construction (Fig. 2), so to operate these plants on schedule requires that projects

commence spending on design now. Few of these projects have certain funding to assist construction, and even fewer have systems to enable commercial operation. National CCS targets with worldwide coordination and exchanges of learning are needed. [Compiled by Y. Bushby (15)]



Second, for insights from operating demonstration plants to be transmitted from the first to the second generation of plants, and to further generations (Fig. 2), detailed commercial information will have to be shared rapidly between companies. In a period of competitive development, such information is normally very tightly controlled by the owners. If these demonstration projects are enabled by public funds, then national governments have some ability to encourage the release of information. The Global CCS Institute in Australia will encourage such information release (30) but can enforce nothing. International agreements are required between governments from the present until 2020.

Third, for rapid learning to help cost reduction, successive generations of equipment have to evolve and improve from the same design. For CCS, there are at least seven different combinations of fuel with the three capture technologies (Fig. 4). Each demonstration project may have distinct transportation systems and individual geological storage sites. Consequently, learning progress in one technology has limited relevance to that of another, and the progress of the "CCS fleet" could be inhomogeneous. So, will CCS globalize? With no price support or communication, CCS will remain limited to interesting but isolated demonstrations. A coherent national and international approach is required to create a new industry that disrupts the status quo.

CCS on a Renewables Electricity Grid

The electricity grid systems of industrialized countries have been developed to distribute reliably from large centralized power plants. Increasing the supply of variable output from wind power to 30% or more produces greater risks of supply interruptions (32). This means that CCS systems will need to be continually responsive to demand, along the whole CCS chain from capture to transport to storage. At extreme times of no wind, 100% reserve capacity will be required from fossil fuel generation.

Periods of no wind are infrequent, but not rare. For example, predictions of the U.K. electricity market price have been made, with a scenario based on an historical calm and cold period during several days in late January 2000 (33). If wind generation in 2030 ceases for a week, then backup gas and coal generation will be needed, at a very high cost. The short-term electricity wholesale price will reach £500 per megawatt hour, compared with a normal price of £50.

For some power plants, the periods of operation could be just months in one year or as few as alternate years. Will CCS expense on such a plant be financially viable? Will CCS be required to operate, even when it may be more profitable to switch off postcombustion CCS to achieve greater electricity output?

Outlook

Power plant capture of CO₂ can technically be enacted now, but with low efficiency and many

energy losses. Current R&D on capture holds very good promise of 20 to 60% improvements in energy efficiency and cost and also of adapted or entirely new capture processes. Transport of CO₂ by pipeline can also be undertaken now. Costs can be reduced if clusters of power plants feed CO₂ into shared transport pipelines. Injection into hydrocarbon fields or aquifers uses established methods and can commence immediately, although the total storage capacity in aquifers is highly uncertain. Worldwide, demonstration projects must use diverse types of storage to test capacity predictions. Public acceptance is also an issue: Opposition has halted several feasible test sites for CCS in Europe. Governments must require heart-and-mind action from developers, several years ahead of applications.

Climate change predictions show that CO₂ reduction must be operating by 2020. Mainstream economic assessments state that CCS is a medium-term, low-cost option that needs to be prepared now (34) and that even a 10-year delay in tackling climate change will be economically serious (35). Yet there is a lack of policies or funds worldwide to support profitable operation of demonstration plants. In the future, industry needs to see and believe in secure, long-term underpinning revenue from low carbon fossil energy, similar to the way that renewable energies have been helped to emerge.

On the 10-year time scale, it is not technology, but legal permission, business development, and public opinion that will determine whether CCS experiments and demonstration plants are built sufficiently rapidly for CCS to be deployed in 2020. On the 20-year time scale, these initial demonstrations must enable a new CCS industry to be born. Low-cost reliable capture at clusters of CCS power plants must emerge, and national pipe networks must be developed, delivering to aquifer storage capacity that must have been validated. CCS also needs to be built and operated in developing economies with high national but low per capita emissions. If CCS is difficult to afford now in Western economies, then it is even more so in India and China. Additional payments for CCS demonstrations will accelerate the above-mentioned actions.

Simply pricing carbon in a market is not enough to encourage CCS or to enforce decarbonization. During peak demand, venting of CO₂ will be commercially beneficial. If the price of carbon is set very high to avoid such effects, that taxes the whole economy, not just dirty electricity. Additional policy levers will be needed to enforce CCS operation. Lessons from previous clean-up technologies applied to power plants—such as SO_x and NO_x removal from flue gases—show that voluntary codes do not work, but clearly signed and enforced rule changes do.

New power plants can now be built "capture ready," to be converted when CCS is established. This is the death-or-glory test of govern-

ments, as there is industry pressure to build new coal and gas plants now, increasing CO₂ emissions, and perhaps convert to CCS later. Substantial difficulties can be anticipated in government-enforced plant-by-plant conversion. Another regulatory route is the introduction of emissions performance standards, expressed as amount of CO₂ per kilowatt-hour of electricity produced. These standards are conceptually simple and directly address the issue. Care will be needed to avoid unintentionally incentivizing gas-fuelled plants, which are not fitted with CCS but lock-in CO₂ emissions. A permitted emission amount decreases through time, enforcing innovation. A key difficulty is that firm rules and dates cannot be applied to technologies that do not yet exist.

Coal and gas combustion can become more sustainable. To change black fuel into green energy, the acceleration and scale-up of CCS is required, from tens of power plants within 5 years, to hundreds of large plants by 2025, and then to thousands of small power plants by 2035. This progression can defer climate change problems and buy time. To do this, bold policies of clear vision to include CCS emissions reductions must be explicit. CCS may be the single most effective and direct climate action available. It is not yet too late, but good words need to be matched by hard actions and good money; the present level of committed funds is too low and needs a 4- to 10-fold increase in order for this climate mitigation to be successful.

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PERSPECTIVE

Amine Scrubbing for CO₂ Capture

Gary T. Rochelle

Amine scrubbing has been used to separate carbon dioxide (CO₂) from natural gas and hydrogen since 1930. It is a robust technology and is ready to be tested and used on a larger scale for CO₂ capture from coal-fired power plants. The minimum work requirement to separate CO₂ from coal-fired flue gas and compress CO₂ to 150 bar is 0.11 megawatt-hours per metric ton of CO₂. Process and solvent improvements should reduce the energy consumption to 0.2 megawatt-hour per ton of CO₂. Other advanced technologies will not provide energy-efficient or timely solutions to CO₂ emission from conventional coal-fired power plants.

Existing coal-fired power plants in the United States have more than 300,000 MW of power capacity, providing about 50% of the total power generated nationally and representing more than 30% of CO₂ emissions. Any reasonable strategy for ameliorating anthropogenic climate change must reduce these emissions without closing these plants. Amine scrubbing is probably the only technology for postcombustion capture of CO₂ that is available to address this problem.

The history of flue gas desulfurization should teach us what to expect in the development and deployment of technology for CO₂ capture. Lime or limestone slurry scrubbing for flue gas desulfurization was first applied at two British plants in 1936 (1), and was identified as an effective technology as early as 1965 (2). However, it was deemed to have unacceptable capital cost, poor reliability, and poor environmental

and—like flue gas desulfurization—was deemed to have unacceptable energy use and costs. It had been successfully applied to gas- (5) and coal-fired plants (6) on a small scale in the early 1980s, but was perceived to be too commercial and not worthy of government support. Since 2000, the U.S. Department of Energy has primarily supported R&D on other advanced technologies for CO₂ capture. However, amine scrubbing will probably be the dominant technology for CO₂ capture from coal-fired power plants in 2030.

CO₂ removal by absorption and stripping with aqueous amine is a well-understood and widely used technology. The basic process, patented in 1930 (7), is one in which CO₂ is absorbed from a fuel gas or combustion gas near ambient temperature into an aqueous solution of amine with low volatility (Fig. 1). The amine is regenerated by stripping with water vapor at 100° to 120°C, and the water is condensed from the stripper vapor, leaving pure CO₂ that can be compressed to 100 to 150 bar for geologic sequestration.

Hundreds of plants currently remove CO₂ from natural gas, hydrogen, and other gases with low oxygen. Four coal-fired plants with power outputs of 6 to 30 MW separate CO₂ from flue gas using 20% monoethanolamine (MEA). More than 20 plants use 30% MEA on gases with substantial O₂ content, including a gas-fired turbine with a flue gas rate equivalent to that of a 40-MW coal-fired power plant that produces flue gas with 15% O₂. More than 10 plants use a proprietary hindered amine, KS-1, with flue gases produced by combustion of clean fuels. Four other demonstration projects using MEA, KS-1, and another proprietary amine at coal-fired plants of 5- to 25-MW capacity will start up in Germany and Alabama, USA, in 2010 and 2011 (8, 9).

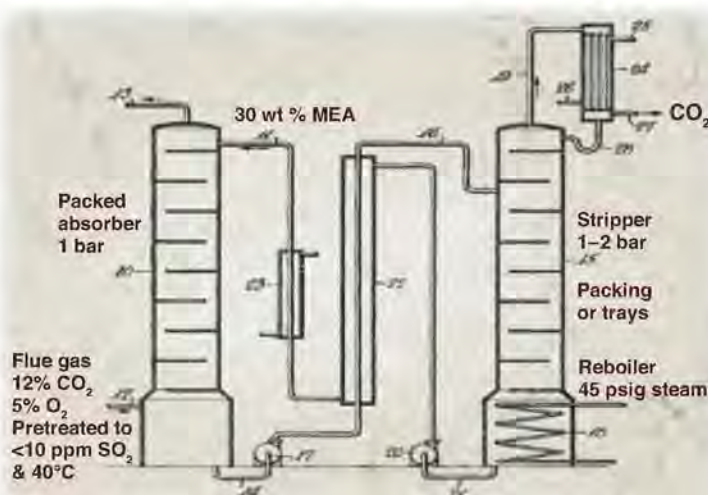


Fig. 1. The amine scrubbing process invented by Bottoms in 1930 (7).

performance, as well as being too commercial, and therefore was considered an unworthy candidate for government-funded research and development. Work on limestone slurry scrubbing continued, nevertheless, gaining increasing attention through the 1970s [e.g., (2, 3)] and beyond, and now it is the dominant technology for flue gas desulfurization.

Amine scrubbing, the technology of choice for CO₂ capture, was first evaluated in 1991 (4)

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A reasonable schedule of process scale-up will permit widespread deployment on plants of 800 MW as early as 2018. This timing will require legislative cap-and-trade and other measures to provide incentive for the expensive, first-of-a-kind demonstration plants. However, limestone slurry scrubbing was demonstrated and deployed in less than 7 years, and amine scrubbing is understood far better than was slurry scrubbing at an equivalent point of its development. It should be possible to install amine scrubbing on an 800-MW plant that would be operational by 2013, if some institution would assume the financial risk and the extra cost of a hastily designed and constructed first-of-a-kind plant.

Economic design studies of scrubbing with aqueous MEA demonstrate both the feasibility of the technique and the uncertainties caused by the lack of experience with full-scale installations. Two studies of MEA scrubbing have been completed on a 450-MW plant (Table 1). In 2001, the design used 20% MEA. In 2006 (10), the study updated the costs from 2001 by employing 30% MEA and better energy integration. The new design reduced energy expended from 0.51 to 0.37 megawatt-hours (MWh) per metric ton of CO₂ removed and the cost of CO₂ removed from \$82 to \$51 per ton. The cost of CO₂ removal is sensitive to the value of replacement power, assumed in this case to be \$80/MWh. The actual cost of replacement power will be specific to the local power grid and is assumed to include the additional cost of CO₂ allowances. In the ERCOT (Electric Reliability Council of Texas) grid, for example, replacement power would be provided by combined cycle generation using natural gas, so the net CO₂ removal for the 2006 case would be 74% and the assumed cost would include any CO₂ penalty associated with gas combustion. Further development of this technology will provide more efficient systems to reduce energy cost, large single absorbers, heat exchangers, and compressors to reduce capital cost, as well as more robust solvents to reduce makeup costs and secondary environmental impact.

Improved solvents and process configurations are expected to reduce the parasitic power demand of CO₂ removal by amine scrubbing from the predicted values of 0.37 to 0.51 MWh/ton CO₂ (10) to 0.19 to 0.28 MWh/ton CO₂ (11, 12), equivalent to 20 to 30% of typical power plant output. The theoretical minimum work is 0.11 MWh/ton CO₂ (9), or about 12%. About half of that energy is low-temperature heat (steam) for the stripper reboiler. The other half is compressor work to provide CO₂ at 150 bar for transport and sequestration. Although no large plants have been built, the estimated energy use with optimized systems has decreased to 27% with 30% MEA (13) and 22% with KS-I (14).

Large absorbers, extensive heat exchange requiring multiple parallel exchangers, and expensive compressor trains produce expected capital

costs of \$700/kW (10) to \$1000/kW (15) of treated capacity (\$106 to \$151 per ton of CO₂ removed over a year), but the cost of these units and other equipment that will be used in parallel should reduce those costs.

Reduced capital and energy costs will come with amines other than MEA, but there cannot be major improvement because the existing designs already provide about 50% thermodynamic efficiency. Concentrated piperazine (PZ) is a thermally resistant solvent with a high heat of CO₂ absorption that is claimed to reduce power loss to

absorber. Advanced amines such as KS-I, PZ (17), and ethyldiethanolamine (18) are resistant to degradation but are more expensive and will require more complex gas pretreating to avoid economic losses from process upsets and the effects of SO₂, NO_x, and fly ash. More expensive solvents, such as ionic liquids, will be more economically sensitive to process upsets and other impurities, even if they are otherwise stable.

Conceptual designs of amine scrubbing systems assume 90% CO₂ removal. Seventy to 95% removal probably represents the range where the cost of

Table 1. Economics of CO₂ capture by MEA scrubbing (10).

Year of design	2001	2006
MEA (weight percent)	20	30
Power used (MWh/ton)	0.51	0.37
@ \$80/MWh (\$/ton CO ₂ removed)	41	29
Capital cost (\$/ton CO ₂ removed per year)	186	106
@16%/year (\$/ton CO ₂ removed)	30	17
Operating and maintenance cost (\$/ton CO ₂ removed)	6	6
Total cost (\$/ton CO ₂ removed)	77	52
Net CO ₂ removal with power replaced by gas (%)	72	74

0.24 MWh/ton CO₂ by operating the stripper at 150°C (12). Vacuum stripping or the use of solvents with a lower heat of absorption will not get the full impact of solvent regeneration by heating to a higher temperature and will require more energy (11, 12). Solvents with greater capacity, such as KS-I, minimize sensible heat losses from heating and cooling the circulating solvent. Solvents with a faster rate of CO₂ absorption, such as methyldiethanolamine with PZ, allow for adequate absorber performance with more dissolved CO₂ in the rich and lean solvent, resulting in reduced energy use by the stripper (12).

Improved process configurations such as absorber intercooling, stripper interheating, flashing systems, and multipressure stripping will also provide reduced energy use, but at the expense of complexity and capital cost (11–13). However, solvent and process improvements are not additive, and we should not expect to do much better than 0.2 MWh/ton CO₂, or about 20% power loss. Claims of greater energy reduction for poorly developed processes must be based on poor understanding of process principles.

MEA is subject to oxidative and thermal degradation (16, 17), but it is the least expensive amine and its losses are expected to be less than \$5/ton CO₂. Impacts of SO₂, NO_x, and fly ash on solvent degradation will be minimized by efficient upstream equipment and including an alkaline scrubber to remove the residual SO₂. Oxidative degradation can be minimized by additives such as free-radical scavengers (16). Thermal degradation can be minimized by operating the stripping systems at lower temperature (e.g., 100°C). Volatile amine emissions in the clean gas are easily avoided by a water wash section at the top of the

CO₂ removal (\$/ton) is minimized. However, there are few fundamental barriers to greater removal.

Advanced separation methods such as membranes and pressure-swing adsorption are likely to be noncompetitive because of compression work. When the driving force for membranes or adsorption is provided by real, intercooled, adiabatic compressors, the expected work is about 0.21 MWh/ton CO₂ (11), with no driving force allowed for the separation itself. Therefore, it is unlikely that real membrane or adsorption systems will compete with advanced amine systems that provide CO₂ at higher pressure with a heat-driven, thermal-swing stripper.

Amine scrubbing is a flexible, tail-end technology that can be tested on existing power plants and applied in increments from 0.2 to 800 MW, as required by development needs and regulations. If the tail-end system is unreliable or lost power production is required to meet peak load demand, the scrubbing system can be turned off. Therefore, the capacity to meet peak demand will not be lost when these systems are retrofitted onto existing plants, although lost power production will have to be replaced from less efficient or more costly existing plants such as gas-fired combined cycles.

The development, demonstration, and deployment of oxycombustion and the integrated coal gasification combined cycle (IGCC) necessarily require and impact a complete power plant. As in the use of fluidized bed combustion and IGCC for SO₂ control, commercialization of these systems will be delayed by the financial, construction, and technical schedules of building successively larger, successful systems. Furthermore, like membrane technology, oxycombustion relies on

mechanical compression to provide the work of separation and will not provide competitive energy consumption. In addition to separating oxygen for the production of CO₂, stoichiometric oxygen (about 20%) must be provided for hydrogen contained in the coal and for the excess required for adequate combustion (about 15%). Consequently, the estimated work for oxycombustion starts at 0.22 MWh. This estimate does not include the irreversibility of the exchangers and distillation columns in the air separation unit, nor does it include the irreversibilities of compressing the excess and leakage air along with the CO₂.

Amine scrubbing will be applied first on large coal-fired boilers with 12% CO₂. It would also be useful with boilers fired by biomass at 14% CO₂, cement plants at 25% CO₂, and steel works with 25% CO₂. It will be less attractive with gas-fired combined cycles at 4% CO₂ or gas- or oil-fired boilers or heaters at 7% CO₂. Amine scrubbing, in use for nearly 80 years, is a robust technique that is ready to be tested and used on a scale

appropriate for CO₂ capture from coal-fired power plants. Process and solvent improvements should reduce the energy use to 0.2 MWh/ton CO₂. Other advanced technologies will not provide solutions as energy-efficient or as timely to decrease CO₂ emissions from conventional coal-fired power plants.

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PERSPECTIVE

Why Capture CO₂ from the Atmosphere?

David W. Keith

Air capture is an industrial process for capturing CO₂ from ambient air; it is one of an emerging set of technologies for CO₂ removal that includes geological storage of biotic carbon and the acceleration of geochemical weathering. Although air capture will cost more than capture from power plants when both are operated under the same economic conditions, air capture allows one to apply industrial economies of scale to small and mobile emission sources and enables a partial decoupling of carbon capture from the energy infrastructure, advantages that may compensate for the intrinsic difficulty of capturing carbon from the air.

Even if we could halt human carbon emissions today, the climate risks they pose would persist for millennia—assuming that we must rely only on natural processes to dissipate our carbon cycle perturbation and the resulting climate changes (1). The impact of carbon emissions persists longer than that of nuclear waste (2), the archetypical long-lived waste product. An immediate emissions halt is essentially impossible, however, and simple extrapolations of emission trends suggest that even with strenuous efforts to limit emissions, CO₂ concentrations in the atmosphere will rise beyond 450 parts per million before mid-century, passing the level commonly invoked as a ceiling above which the risk of dangerous climate change becomes unacceptably high. Moreover, the climatic response to elevated CO₂ concentration is uncertain, so a small risk of catastrophic impacts exists even at today's concentration, and that risk grows

monotonically as emissions continue to drive up the atmospheric CO₂ burden.

Technologies for decarbonizing the energy system, from solar power to the capture of CO₂ from the flue gases of coal-fired power plants, can cut emissions but they cannot reduce the climate risk posed by the carbon we have already added to the air. It may be possible to increase Earth's reflectivity, engineering a cooling that counteracts the CO₂-driven warming (3, 4). Although climate engineering may be important for managing climate risk, it cannot eliminate the long-term climate and geochemical risks posed by elevated CO₂. It is therefore in our interest to have a means to reduce atmospheric CO₂ concentrations in order to manage the long-run risks of climate change. Unless we can remove CO₂ from the air faster than nature does, we will consign Earth to a warmer future for millennia or commit ourselves to a sustained program of climate engineering.

Air capture is an industrial process that captures CO₂ from ambient air, producing a pure CO₂ stream for use or disposal (5, 6). It is one of an emerging set of technologies for remov-

ing CO₂ from the atmosphere that includes biomass energy with CO₂ capture, along with various means of accelerating geochemical weathering (7, 8).

Over the long run, the ability to remove CO₂ from the air should be viewed as an essential tool in our kit for managing carbon-climate risks. We therefore need, at the minimum, a serious long-term exploratory research effort to develop air capture along with other direct methods for removing CO₂ from the atmosphere.

In the near term, efforts to limit climate risk should focus on reducing emissions. Capturing CO₂ from the air, where its concentration is 0.04%, might well seem premature, given that there is still no power plant in which CO₂ is captured from the full exhaust stream. One might well conclude that there is little reason to develop and deploy air capture in the coming decades, before we can reduce emissions to the near-zero level where the ability to drive global emissions negative becomes relevant. The global energy system is marvelously diverse, however, and in



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that diversity there are important niches where air capture might play a role in reducing emissions in the near term, long before we are able to bring emissions near zero.

Near-term development of air capture only makes sense if it can be realized at a sufficiently low cost. Two factors make capture from air more difficult than from exhaust streams: first, the higher thermodynamic barrier due to the lower concentration of CO₂ in air; and second, the energy and materials cost of moving great quantities of air through an absorbing structure. These factors present a smaller barrier than one might expect from the 300:1 difference in partial pressure between CO₂ in power plant exhaust and in the ambient air. The energy required to separate gases scales as the log of partial pressure, and if one includes the energy needed for compression to pipeline pressures, the thermodynamic minimum energy required for air capture is only about 50% larger than for a post-combustion process (5).

It is nevertheless clear that air capture will always cost more than post-combustion capture from power plants if both facilities are designed and operated under the same economic conditions. Economics tells us, however, that there is surprising value in the freedom to build a capture plant where the costs of construction and operations are cheap. Moreover, air capture allows one to apply industrial economies of scale to a myriad small and hard-to-control CO₂ emitters such as aircraft and home furnaces. Finally, air capture enables the partial decoupling of carbon capture from the energy infrastructure, easing the constraints that arise when new energy technologies must be integrated into the existing infrastructures and making it easier to build a capture plant near the best sequestration sites (5, 6, 9).

In combination with the carbon market, air capture might allow carbon to be physically removed in the most cost-effective circumstances, eliminating the necessity for controlling the most expensive sources (such as aircraft) even if it is necessary to reduce net carbon emissions to zero. Air capture thus enables a physical carbon arbitrage distinct from the arbitrage achievable by carbon markets. The near-term value of air capture is thus rooted in its ability to exploit niches opened by the technological and economic diversity of our energy systems.

The benefits of air capture are moot, however, if the costs are unacceptably high. The cost of air capture is uncertain and hotly disputed. Some have argued that the costs would be prohibitively high (10), or that investing funds in research on air capture is a mistake because it diverts attention from more important areas (11). In sharp contrast, others have argued that air capture might be comparatively inexpensive and that it could play a central role in managing CO₂ emissions (6, 12).

Air capture is neither a silver bullet nor a hopeless dream: It is simply another chemical engineering technology. Disputes about cost can

only be resolved by developing a few air capture technologies to the point where they can be independently evaluated. Costs cannot be understood until specific processes are developed to a far greater technical depth than has been achieved to date. As with other energy technologies, it is not possible to determine the cost through small-scale university research alone. Instead, costs will only become evident with pilot-scale process development and when costing can be performed by contract engineering firms with relevant expertise.

Current research on air capture technology is centered on a handful of academic groups or small start-up companies. At least two groups are using a solid sorbent system that is regenerated in situ. One method uses ion exchange membranes with humidity-swing regeneration (6, 13), whereas the other uses solid amines on a mesoporous silica substrate similar to those that are being developed for CO₂ capture from power plants (14). Most of the other methods start with the absorption of CO₂ by an alkaline aqueous solution, which typically makes the capture step cheaper but raises the cost of regeneration. The method pursued by my group, for example, captures CO₂ with alkali hydroxide solutions, which are strongly absorbing, contamination-insensitive, and can have minimal water loss, factors that lower the cost and technical risk of the absorption step. The tradeoff is the large energy demands of the regeneration step, which is a variant of the caustic recovery processes used in the pulp and paper industry, chosen to maximize scalability and minimize technical risk (15, 16). Our baseline system uses natural gas as an energy source, but others are developing solar kiln technology for air capture (17). Finally, at least two other groups are using electrochemical cells to regenerate the spent caustic solution (18), and another aims to reduce the cost of regeneration by using a much weaker hydroxide solution to lower the regeneration energy, in combination with catalysts to overcome inherently slower CO₂ uptake of the weaker absorbent (19).

There are no government funding programs that specifically target the development of air capture, and I estimate that the total annual expenditure for these efforts is currently less than \$3 million per year, of which more than half is private. A more substantial investment of government R&D funding is warranted for at least three reasons. First, early estimates suggest that air capture will be competitive with technologies that are getting large R&D investments. For example, the cost of cutting CO₂ emissions by displacing carbon-intensive electricity production with roof-mounted solar photovoltaic panels can easily exceed \$500 per ton of CO₂. Yet even skeptics (10) suggest that a straightforward combination of existing process technologies could probably achieve air capture at lower cost. And the fact that several groups have raised private money for commercialization suggests that there

are investors who believe that it is possible to develop technologies to capture CO₂ from air at costs closer to \$100 than \$500 per ton of CO₂.

Second, air capture offers one route to make carbon-neutral hydrocarbon fuels (CNHCs) for vehicles by using captured CO₂ to make synthetic fuels. Deep reductions in emissions from the transportation sector will require a change in vehicle fuel. Each of the three leading alternative fuel options—electricity, biofuels, and hydrogen—faces technical and economic hurdles that preclude major near-term reductions in transportation emissions. CNHCs represent a fourth, fundamentally different alternative: a method for converting primary energy from carbon-free sources such as solar or nuclear power into high-energy-density vehicle fuels compatible with the current vehicle fleet. It is unclear whether CNHCs will be competitive with the three leading alternatives, but they are promising enough to warrant R&D support on a par with efforts aimed at advancing the alternatives (20).

Finally, air capture allows negative global CO₂ emissions. Although this is a distant prospect, it is important because it represents one of the few ways to remediate human impact on the carbon cycle, an impact that is otherwise all but irreversible (1, 5).

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PERSPECTIVE

Onshore Geologic Storage of CO₂

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The possibility that substantial quantities of CO₂ can be injected into subsurface porous rock formations has been investigated sufficiently to show that pore space available to contain the CO₂ is abundant. Multiple rock types and physical mechanisms can be used to trap the CO₂ indefinitely. With careful site selection and operations, leakage to the near-surface region can be avoided. The next step is to test these injection processes at the scale of a large power plant.

One option for reducing CO₂ emissions from fossil fuel combustion to the atmosphere is to capture and store the CO₂ in porous rocks in the deep subsurface. Large volumes of pore space that might be used to contain CO₂ exist in sedimentary rocks distributed widely around the world, especially in the U.S. Estimates of worldwide potential storage capacity range from 1700 to almost 11,000 gigatons of CO₂ (GtCO₂) (1, 2), and more recent estimates for the U.S. alone show potential storage capacity of 2020 to 14,220 GtCO₂ (3, 4). The wide ranges of the estimates reflect differing assessment methodologies and assumptions about the types and locations of geologic formations included in the assessments (5). Not all potential storage resources will turn out to be suitable, but even so, the potential capacity is large enough that storage of sizable quantities of CO₂ can be contemplated. About 95% of large point sources of CO₂ in the U.S. are within 80 km of a potential storage formation (2).

What rock formations might be suitable for storage? The best choices will be at depths below ~800 to 1000 m, where the CO₂ density is high enough (~500 to 700 kg/m³) to limit the storage volume required. An essential feature is the presence of low-permeability formations above the storage zone (known as seals or caprocks, often shales or evaporites) that prevent vertical flow of CO₂ to the near-surface region. Suitable formations will be large enough that tens of millions of metric tons of CO₂ can be stored in a project lasting the multidecade lifetime of a power plant, and they will

be permeable enough that the CO₂ can be injected at reasonable rates through a modest number of injection wells. Suitable sites will avoid leak hazards of nonsealing faults or wells that have not been properly plugged and

decades of experience transporting large quantities of CO₂ through 5600 km of pipelines and injecting it into the subsurface has been accumulated in this location (6). CO₂ is used for EOR because at high pressure, transfer of components from oil to supercritical CO₂ creates mixtures that can displace oil efficiently in the portion of the formation swept by CO₂. Several of the tests of CO₂ storage worldwide involve EOR (7). CO₂ EOR has always been limited by availability of CO₂ at a cost low enough to allow economic projects: Abundantly available CO₂ with a high price of emissions would make more oil reservoirs candidates for CO₂ EOR, though other constraints, such as field size and availability of infrastructure for delivery and distribution of CO₂, will also limit potential applications.

Oil and gas reservoirs are present in some locations near large sources of CO₂ (in the Gulf

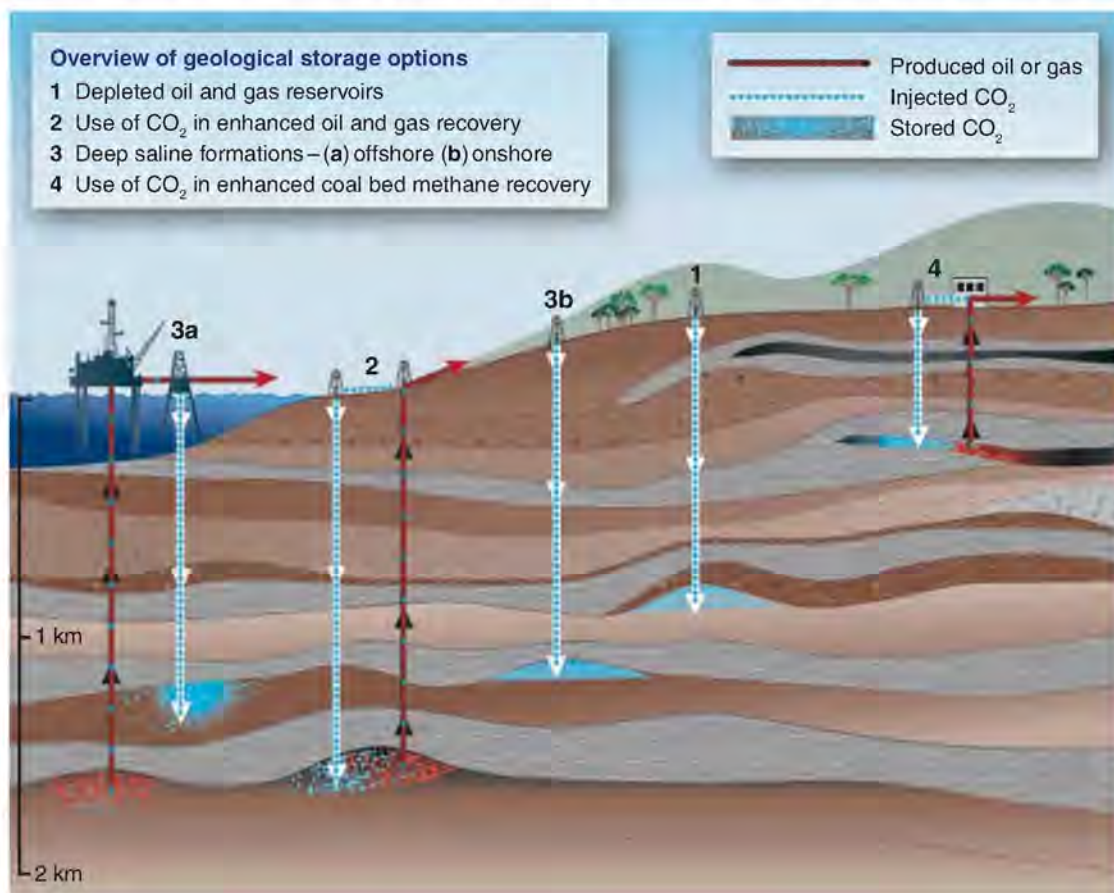


Fig. 1. CO₂ storage options. Options include oil and gas reservoirs, deep formations that contain salt water, and deep coal beds. [Source: Fig. TS-7, IPCC Special Report on Carbon Capture and Storage]

abandoned and will have sufficient surface area available for the required facilities.

Oil and gas reservoirs are obvious potential choices (Fig. 1). The fact that buoyant oil and gas have been retained in them for geologic periods of time is a direct indication that a seal exists. About 30 megatons of CO₂ (MtCO₂) are injected into oil reservoirs in west Texas each year for the purpose of enhanced oil recovery (EOR). Three

Coast region of the U.S., for example), but their overall capacity is expected to be modest (47 to 138 GtCO₂ in the U.S.) (2–4). In other locales, deep formations that contain nonpotable salt water are the candidate storage settings. 1800 to 13,910 GtCO₂ of the estimated onshore capacity for CO₂ storage in the U.S. is contained in these deep saline formations (2–4). Injection of CO₂ into deep saline formations is being tested at the commer-



cial scale (~1 MtCO₂ per year) with the use of CO₂ that is separated from natural gas at the Sleipner field in the North Sea, the In Salah field in Algeria, and the Snohvit field off the northern coast of Norway (7). These projects inject CO₂ at a scale of about one-quarter to one-third of that required for a large coal-fired power plant.

What happens when the CO₂ is injected in those settings? At the subsurface temperature and pressure, the CO₂ is typically a supercritical phase that is less dense than brine or oil, but more dense than natural gas. In liquid-filled formations, the CO₂ will flow away from the injection well under the imposed pressure gradient in a relatively thin gravity tongue just beneath the caprock, though heterogeneities in the permeability of the rocks will also influence where the CO₂ flows. The injected CO₂ will then interact with the fluids and minerals present. The pressure will rise in the formation as injection proceeds, and an important determinant of the total capacity of a deep formation will be the maximum pressure rise that can be tolerated without breaching the seal rocks or activating faults that might conduct flow (8, 9).

What physical mechanisms act to prevent escape of the CO₂ from the storage formation and on what time scales? Seals prevent vertical flow immediately. CO₂ is relatively soluble in brine, and the resulting brine mixture is slightly more dense than brine alone. At typical subsurface conditions, about 20 volumes of brine are required to dissolve 1 volume of CO₂. Low-viscosity CO₂ displaces brine relatively inefficiently, however, so that sufficient brine to dissolve the CO₂ will remain in the pore space. Dissolution begins immediately when CO₂ contacts brine, creating a small driving force for downward unstable flow of the denser brine mixture (10). Once all of the CO₂ is dissolved, the driving force for upward migration of CO₂ is eliminated, though transport due to brine migration is still possible (11). When brine invades zones that are filled with CO₂, as will happen after CO₂ injection has ceased because of gravity relaxation or if brine is injected after the CO₂, capillary forces create a pore scale instability that snaps off isolated bubbles of CO₂. Once these bubbles are created, they cannot move unless very high pressure gradients are applied, and hence, the CO₂ is immobilized while it continues to dissolve slowly. Estimates of the time scales for trapping and dissolution suggest that whatever trapping is going to happen will do so in a few injection time periods (typically 30 to 40 years), and dissolution will also be completed on a time scale of centuries (12). These immobilization mechanisms act in parallel over the life of a storage project to increase storage security with time (1).

Deep, unmineable coal beds are also possible storage locations, with potential U.S. capacity of 30 to 173 GtCO₂ (2–4). Flow of injected CO₂ takes place in naturally occurring fractures, and adsorption of CO₂ in the coal matrix begins immediately as diffusion delivers CO₂ to adsorption

sites. Potential vertical flow of CO₂ through the fractures means that a seal must be present in this setting as well. When CO₂ adsorbs, it replaces CH₄, and the desorbed CH₄ can migrate to the fractures and be recovered. The use of CO₂ for enhanced gas recovery has been demonstrated at the laboratory scale (13) and tested in a limited way in the field (7). However, adsorption of CO₂ reduces permeability, and that considerably reduces the rate at which CO₂ can be injected, a problem that has been observed in field tests.

Shales that are rich in organic material may also have potential for CO₂ storage (14). Recent growth in natural gas production has come from wells drilled in these shales, where horizontal wells and fracturing technologies have been used to increase gas flows. Limited experimental evidence suggests that, whereas the amount of CO₂ that adsorbs in shales is lower than in coals (14), the shale deposits are large enough that one study estimated potential capacity as 107 GtCO₂ (4). As in coals, the challenge will be to establish flow paths that can deliver the CO₂ in quantity to adsorption sites and collect any desorbed CH₄ (15).

On still longer time scales, thousands of years in many settings, chemical reactions can take place that immobilize the CO₂ in the form of minerals (16). Which reactions take place and what minerals form depend strongly on the chemistry of the brine and the minerals and cements present in the porous rock. Dissolved CO₂ in brine reduces pH and forms carbonate and bicarbonate ions that can react to dissolve calcium carbonate or silicate minerals (17) or mobilize other trace metals such as manganese (18). Dissolution of silicates can raise the pH enough to precipitate calcium, iron, or magnesium carbonates and other minerals. A version of these mineralization reactions has been proposed for basalts, which are widely distributed on Earth and contain more of the reactive elements than do typical sedimentary rocks (17). Whether CO₂ could be injected and contained in basalts for the times required to react the CO₂ is still under investigation.

Careful characterization of the subsurface, good design of the injection project, and careful field operations will be required for safe conduct of large-scale carbon capture and sequestration (CCS) projects. At low concentrations, CO₂ is not dangerous. For example, a large coal-fired power plant (for instance, 500 MW) emits ~3 MtCO₂ per year to the atmosphere, and mixing of the N₂/CO₂ effluent with the atmosphere quickly reduces the local concentration near the stack. At high concentrations, however, CO₂ is an asphyxiant and is toxic. A concentration of 4% CO₂ in air is immediately dangerous to human health, and the National Institute for Occupational Safety and Health and Occupational Safety and Health Administration limit for exposure is 5000 parts per million. Thus, leakage to the surface, where dense CO₂ could collect in a depression at times of zero or low wind (19), or to the near-surface region, where water supplies could be affected,

must be avoided. Wells are the most likely leak paths because they must penetrate the storage zone (19). Well pressures and pressures in formations above the storage zone are easily monitored, however, and well problems are corrected routinely in oil and gas operations.

Migration of CO₂ in the subsurface can also be monitored (1). Seismic methods (both surface reflections and tomography) have been used in field tests to detect the movement of CO₂ in the subsurface and should also be able to detect leaks out of zone. Gravity methods and deformation measurements (synthetic aperture radar, tiltmeters) can provide somewhat lower-resolution indications of migration. Tracers, fluid composition measurements, electromagnetic methods that detect changes in fluid conductivity, soil gas, and eddy covariance methods for air sampling also can be used where appropriate. Because the probability of leakage will decline after injection ceases, as the pressure gradient in the storage zone decays and trapping, dissolution, and reaction immobilize CO₂, storage security will increase with time, and the need for active monitoring will decline (1).

Experience with CO₂ injection in EOR and aquifer settings is accumulating at sites around the world, and many more tests are in various stages of planning (7). The component technologies for CCS have been demonstrated at the commercial scale, though integration at the scale of a large power plant (500 MW or more) has not yet been demonstrated. An important next step will be to test geologic storage in a larger variety of geologic settings with CO₂ from power plants and other sources, such as refineries, chemical, cement, ethanol, or natural gas processing plants, that release relatively pure CO₂ now.

It is important to recognize that the infrastructure that will be required to substantially reduce emissions is very large: Subsurface injection of 1 GtCO₂ per year, about one-sixth of the U.S. CO₂ emissions from energy use, is the equivalent in subsurface volumes of 25 to 35 million barrels per day of injection—about 50% more than the volume of U.S. daily petroleum use. The many tests of CCS now being planned for a variety of CO₂ separation schemes and geologic settings are an essential next step to determine whether CCS can be one element in the portfolio of ways to reduce CO₂ emissions.

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PERSPECTIVE

Storage of Carbon Dioxide in Offshore Sediments

Daniel P. Schrag

The battle to reduce greenhouse gas emissions and prevent the most dangerous consequences of climate change will be waged across multiple fronts, including efforts to increase energy efficiency; efforts to deploy nonfossil fuel sources, including renewable and nuclear energy; and investment in adaptation to reduce the impacts of the climate change that will occur regardless of the actions we take. But with more than 80% of the world's energy coming from fossil fuel, winning the battle also requires capturing CO₂ from large stationary sources and storing that CO₂ in geologic repositories. Offshore geological repositories have received relatively little attention as potential CO₂ storage sites, despite their having a number of important advantages over onshore sites, and should be considered more closely.

There are some good reasons why carbon capture and storage (CCS) is attractive as a climate change mitigation strategy: A large fraction of CO₂ emissions comes from relatively few sources. In 2007, there were 2211 power plants that emitted at least 1 million metric tons of CO₂ per year; 1068 were in Asia (559 in China), 567 in North America (520 in the United States), 375 in Europe, and 157 in Africa (1). Together, these power plants released 10 billion metric tons of CO₂, or one-third of global emissions. If these plants could be retrofitted or rebuilt with capture technology, and if appropriate storage locations could be identified, then CCS would allow the world to reduce emissions while still using its fossil fuel reserves, at least until long-term substitutes can be developed. Widespread adoption of CCS in the United States and Europe over the next few decades would make it more likely that similar systems will be deployed in other countries, especially in rapidly growing economies with high present and future CO₂ emissions.

For the past 13 years, a Norwegian oil company has been running an experiment that leads

the world in showing how CCS can play an important role in a broad portfolio of climate-mitigation strategies. Since 1996, in the North Sea, halfway between Scotland and Norway and far out of sight of land, StatoilHydro has been quietly injecting 1 million metric tons of CO₂ per year into a sandstone reservoir that lies 1000 m below the sea surface (Fig. 1). The CO₂ comes from a natural gas deposit called the Sleipner field. Extracting the gas for transport back to land requires separating the CO₂ anyway, so, faced with a carbon tax from the Norwegian government, StatoilHydro decided to turn a liability into an opportunity. As the longest-running, commercial-scale carbon-injection site, Sleipner serves as a demonstration for those who believe that this approach can help decarbonize our energy economy and serves as a laboratory for understanding how CO₂ migrates through the subsurface after injection, using techniques such as time-lapse seismic surveys (2).

One million metric tons of CO₂ per year is a start, but the demand for CCS is much more, perhaps as much as 10 billion metric tons of CO₂ per year or more. Finding storage locations for all that carbon will not be easy. Such amounts far exceed the capacity of old oil and gas fields, which will be among the first targets for sequestration projects because of additional revenues earned from enhanced oil recovery

(EOR). Safe storage of CO₂ in a geologic formation requires a good reservoir with adequate porosity and permeability and thick, impermeable cap rocks that will prevent the CO₂ from escaping. Luckily, geologic storage does not have to last forever—only long enough to allow carbon sinks in the natural carbon cycle to reduce atmospheric CO₂ to near preindustrial levels [roughly 4000 years (3)].

Most investigations of CO₂ storage in the U.S. focus on terrestrial geologic formations, in particular, deep saline aquifers. Another approach to CO₂ storage is injection offshore into marine sediments, similar to what is done at Sleipner. Both approaches will ultimately be needed to accommodate all the large stationary sources of CO₂ in the United States, but there are several reasons why storing CO₂ in geologic formations offshore may be easier, safer, and less expensive than storing it in geologic formations on land, at least during the early days of commercialization.

CO₂ storage in offshore geologic formations is not ocean storage. The CO₂ injected into ocean sediments is stored deep beneath the ocean, avoiding the hazards of direct ocean injection, including effects on ocean ecology. Furthermore, marine sediments offer enormous storage potential. For example, a series of Cretaceous sandstones off New Jersey (4), which were drilled extensively in the 1970s as part of the oil and gas exploration program, appear to have the capacity to store at least several hundred billion tons of CO₂: enough to dispose of all the CO₂ from power plants within 250 km of the coast from Maryland to Massachusetts for the next century. Like on land, offshore storage sites require reservoirs with high permeability (typically sandstones), and thick, low-permeability cap rocks to prevent CO₂ from escaping (typically mudstone and shale). However, if one could find reservoirs with adequate permeability in deep water (that is, below 3000 m), the high pressure and low temperature would render the CO₂ denser than seawater, making the cap rock less important (5), although high-permeability sandstones are uncommon in deeper water environments. In many marine settings, the upper 1000 m of sediment, if it is dominated by clay, is unconsolidated, which means that faults and fractures do not persist as high-permeability pathways for CO₂ escape.

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Another advantage of offshore carbon storage is the potential to manage pressure within the geologic formation. Carbon storage is different from EOR in that EOR involves both the injection of CO₂ and the extraction of fluid—usually a mixture of water, CO₂, and oil (the CO₂ is usually reinjected). Injection of CO₂ into saline aquifers on land, however, without extraction of the saline water, increases pore pressures and changes the way CO₂ migrates in the subsurface. If the permeability of the reservoir is extremely high, then management of pressure is not a problem, because pressure transients near to the injection well are rapidly dispersed. As the scale of CCS increases, with as much as 100 million tons per year injected within a single formation, management of subsurface pressure will become a greater and greater challenge. Indeed, displacement of saline water and pressure management may prove the greatest overall challenge for CO₂ storage.

This is where CCS in marine sediments offers an enormous advantage. An important difference between offshore and onshore storage of CO₂ is the nature of the fluid inside the geological formation. In sedimentary basins on land, where CO₂ sequestration has been proposed, the pore fluids are generally much saltier than seawater because of hydrologic cycling and evaporation over geologic time. The chemistry of these pore fluids is quite different from that of seawater because of chemical reactions in the sedimentary basin, and the pore fluids frequently contain high concentrations of toxic metals such as arsenic or lead. It would be undesirable to displace such pore fluid from the formation, similar to producing oil during EOR, and then discharge it, because one would merely be trading one disposal problem for another.

In most marine sediments, the pore fluid is much more similar to seawater, as it is essentially ancient seawater, modified slightly by diagenetic reactions and slow diffusive transport. Along continental margins with moderate organic matter content, the major differences from seawater are the presence of sulfide instead of sulfate and an increase in calcium with a corresponding drop in magnesium. Even when the salinity is high because of the influence of evaporites, the overall chemistry is not substantially different from that of seawater. As long as there are not high concentrations of oil or other hydrocarbons, the release of marine pore fluids to seawater to accommodate CO₂ injection will

not cause any harm to the marine environment, as stipulated by the Environmental Protection Agency (EPA) regulations for oil platforms for their discharge of produced water to the ocean. The ability to manage pressure by drilling additional wells to release pore fluid to the ocean not only provides extra safety to prevent a fracture from

recently exist for leasing land offshore for CO₂ injection, the Minerals Management Service within the Department of the Interior leases land for industrial operations, such as oil and gas extraction, and will probably provide similar oversight for CCS. Offshore storage also offers a similar advantage in locating pipelines for CO₂ transport, which are difficult to site in heavily settled areas.

In general, working in the offshore environment is more expensive; drilling rigs, seismic surveys, and well manifolds are all much more expensive than for a comparable situation on land. The overall economics of CCS, however, make offshore storage very attractive. CCS costs are dominated by the cost of capture and compression. If offshore sites are easier to permit and easier to finance, after 13 years of demonstration at Sleipner, then the extra cost for characterization is more than justified. In addition, the high density of people near the coasts in U.S. regions such as the Northeast and California, combined with high electricity prices and stricter-than-average environmental regulations such as the Regional

Greenhouse Gas Initiative, make these regions early targets for commercial power development involving CCS.

With all the advantages, including enormous capacity and the ability to actively manage pressure, CO₂ injected deep beneath the ocean floor is probably the best option for large population centers near the coast. It may take a long time before people are comfortable storing vast quantities of CO₂ near to where they live, even if the best science suggests that it is perfectly safe. Eventually, carbon storage fields will be needed in many different regions, and many of these sites will be onshore. But until there is more experience with CO₂ injection on larger and larger scales, it seems that StatoilHydro has the right idea.



Fig. 1. Since 1996, StatoilHydro has been separating 1 million metric tons of CO₂ per year from a natural gas platform in the Sleipner Field in the North Sea and injecting it into a sandstone reservoir. Seismic monitoring has shown that the CO₂ is safely contained beneath a thick sequence of impermeable shales. [Photo: Dag Myrestrand/StatoilHydro]

allowing CO₂ to escape to the surface, but also allows for much more careful control and monitoring of the CO₂ plume during injection. This also allows a much higher fraction of the pore space to be used, reducing the footprint of an individual injection field.

Beyond the technical advantages, there are numerous social, political, and economic reasons why offshore storage of CO₂ is likely to be important during the early deployment of CCS, at least in heavily populated areas. In the United States, locating storage sites near populated areas where most CO₂ is created may be practically impossible, at least under current regulatory practices. In Europe, the situation is similar. For example, the town council of Barendrecht in the Netherlands recently opposed the permitting of a CO₂ storage site, arguing that the developers should not conduct an experiment underneath a place where so many people live. In contrast, offshore storage sites are in nobody's backyard.

In the United States, there is a debate over whether the surface landowner, the state, or the federal government owns the pore space within the storage reservoir. For offshore storage, there is no debate: Beyond 3 miles, the federal government owns the land. New EPA regulations for CCS focus on contamination of drinking water aquifers, which is not an issue for marine sediments far offshore. Although no regulations cur-

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Oceanic Spawning Migration of the European Eel (*Anguilla anguilla*)

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European eels (*Anguilla anguilla*) undertake a ~5000-km spawning migration from Europe to the Sargasso Sea (1), although details of the migration remain unknown. Satellite tracking enables investigation of migratory behavior of large ocean-dwelling animals (2), but tag sizes have precluded tracking smaller animals like European eels. Here, we present information about the spawning migration of European eels based on a miniaturized pop-up satellite archival transmitter (PSAT). The experiment fell short of revealing the full migration to the Sargasso Sea, but the tags tracked eels up to 1300 km from release and provided unique behavioral insights.

Transmissions were received from 14 of 22 tagged silver eels released on the west coast of Ireland in October and November 2006 (table S1). Eels migrated southwest, suggesting a route against the prevailing shelf edge and Atlantic drift currents and toward the Canary and Azores current systems (Fig. 1A). The horizontal net migration speed varied from 5 to 25 km day⁻¹ (mean of 13.8 km day⁻¹), much lower than required [35 km day⁻¹ (1)] to reach the Sargasso

Sea for spawning in April (table S1). This may reflect drag from the PSAT. However, the inferred speed corresponded to results from eels tagged with much smaller archival or acoustic tags in coastal areas (1) and to PSAT studies of much larger long-finned eels (*A. dieffenbachii*) in the Pacific Ocean (3). In consequence, our data are consistent with a hypothesis (4) suggesting that eels gain speed and increase travel efficiency by entering the south- and west-flowing currents that begin west of Africa and continue as part of the subtropical gyre system to the Caribbean.

The habitat use revealed by depth and temperature data showed that migrating eels encountered a diverse range of environments (fig. S1), consistent with ARGO data collected from the same region and time period (fig. S2). When eels moved into the mesopelagic zone they all undertook distinct diel vertical migrations (DVMs), predominantly between depths of 200 and 1000 m. DVM was typified by two tag records (Fig. 1B; all following results refer to these tags). During night, eels occupied shallow warm water (daily average = 282 ± 138 m, 11.68° ± 0.48°C). At

dawn, eels made a steep dive into the cool dispersive zone (daily average = 564 ± 125 m, 10.12° ± 0.89°C, minimum observed = 7.1°C). At night, they ascended steeply back into the upper layer.

DVM allows pelagic organisms to avoid exposure to predators during the day and maximize feeding time at night (5). Predator avoidance may explain the deeper depths during the day, but eels do not feed during the spawning migration. We hypothesize that the observed DVM reflects thermoregulation. The daily ascent into shallower warm water may serve to maintain sufficiently high metabolism and swimming activity (1), whereas descent to deeper waters may permit the eels to keep their average temperature below 11°C, delaying gonadal development (6) until reaching the Sargasso Sea. This potential delay of the maturation may prove especially important when eels encounter higher surface temperatures during later stages of the migration.

Further technical improvements of PSAT tags render it realistic to record the entire spawning migration to the Sargasso Sea.

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8. This work was funded by the Villum Kann Rasmussen Foundation, Elisabeth and Knud Petersen's Foundation, and the European Union FP7 (EELIAD, grant no. 212133). This is paper no. 40 of the Danish Galathea 3 Expedition.

Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5948/1660/DC1
Materials and Methods
Figs. S1 to S3
Table S1

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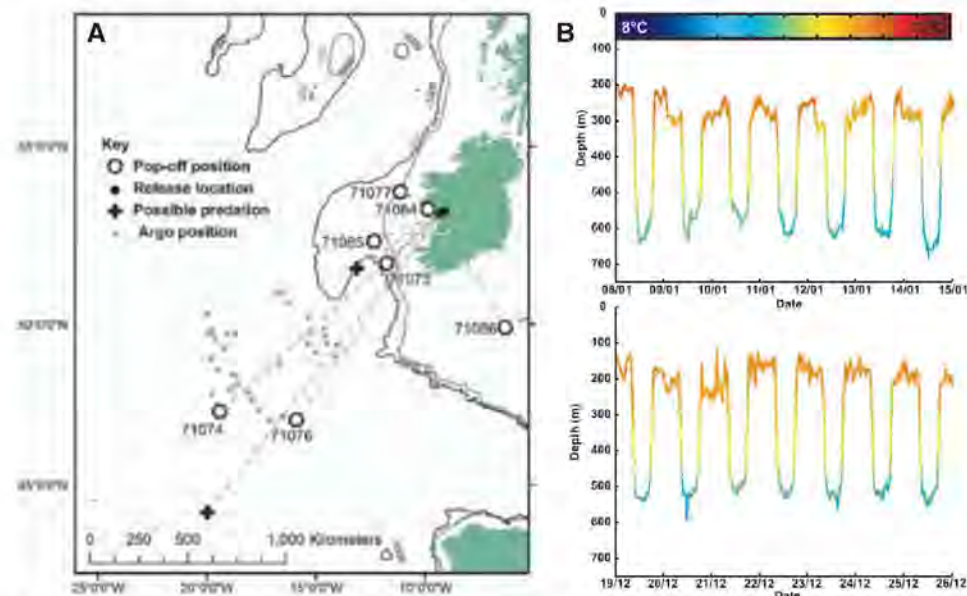


Fig. 1. (A) Map showing pop-up positions (± 1 km, determined by Doppler shift) and positions of data extractions from the ARGO database used as corroboration (7). Pop-up positions for 71077 and 71086 are unreliable because of extensive drift before being picked up by the satellites. **(B)** Oceanic diel vertical migration of two eels, 71074 and 71076. Data from tag 71074 (January 2007) are shown in the top graph, and data from tag 71076 (December 2006) are shown in the bottom graph. Depth values are colored by temperature, over a week-long period.

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Formation of ArF from LPdAr(F): Catalytic Conversion of Aryl Triflates to Aryl Fluorides

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Despite increasing pharmaceutical importance, fluorinated aromatic organic molecules remain difficult to synthesize. Present methods require either harsh reaction conditions or highly specialized reagents, making the preparation of complex fluoroarenes challenging. Thus, the development of general methods for their preparation that overcome the limitations of those techniques currently in use is of great interest. We have prepared [LPd(II)Ar(F)] complexes, where L is a biaryl monophosphine ligand and Ar is an aryl group, and identified conditions under which reductive elimination occurs to form an Ar-F bond. On the basis of these results, we have developed a catalytic process that converts aryl bromides and aryl triflates into the corresponding fluorinated arenes by using simple fluoride salts. We expect this method to allow the introduction of fluorine atoms into advanced, highly functionalized intermediates.

A large number of pharmaceuticals and agrochemicals contain fluorinated aromatic (Ar-F) groups, which enhance solubility, bioavailability, and metabolic stability compared with nonfluorinated analogs (1–4). Furthermore, radioactive ^{18}F -labeled organic compounds are also widely used as contrast agents for positron emission tomography (PET) (5, 6).

However, traditional methods for the introduction of a fluorine atom into an aromatic framework usually require harsh conditions that are incompatible with many functional groups. Such methods include direct fluorination (7), the conversion of amines via the aryldiazonium salt with HBF_4 (Balz-Schiemann reaction) (8), and the nucleophilic substitution of electron-poor bromo- or chloroarenes with KF (Halex reaction) (9), as well as the more recent transformation of aryl iodides with CuF_2 (10). A modified Balz-Schiemann process, of particular use for PET (11), uses arylidonium salts that are produced under highly acidic or oxidizing conditions (12). In a recent important advance, the Halex reaction was performed at room temperature by using anhydrous tetrabutylammonium fluoride, but the substrate scope was limited and the fluoride source is not readily amenable to the preparation of ^{18}F -labeled compounds (13). Because of these limitations, fluorine atoms are often introduced to aromatic compounds early in synthetic sequences and before the introduction of substantial molecular complexity, which greatly increases the difficulty of accessing target molecules.

Recently, transition-metal promoted Ar-F bond formation has been achieved with use of electrophilic “ F^+ ” reagents such as Selectfluor (Air Products and Chemicals, Incorporated, Allentown, PA) or *N*-fluoropyridinium salts (14–20). These interesting reactions are believed to proceed via high-valent Pd or Ag intermediates and have been used to access highly functionalized aryl fluorides. However, these reactions have some limitations with respect to preparative chemistry. In many cases, stoichiometric amounts of the transition metal must be used. In the reported examples that proceed with a catalytic quantity of metal, specific directing groups on the substrate are required to facilitate a C-H activation process, thus diminishing the general applicability of the methods (14, 15, 21). An additional drawback of this approach is that electrophilic ^{18}F reagents are not available with high specific activity, lessening the utility of these methods for PET applications (12, 22).

In light of the importance of fluorinated arenes and the practical limitations of current methods for their preparation, the metal-catalyzed conversion of an aryl halide or sulfonate (e.g., triflate, abbreviated as OTf) with a nucleophilic fluorine source (such as an alkali metal fluoride) to yield the corresponding aryl fluoride is a highly desirable transformation (Fig. 1). For a process operating at reasonable temperatures and in the absence of electrophilic reagents, high functional group compatibility and a wide substrate scope might be expected. This is of particular importance in the preparation of biologically active compounds, where often late-stage modifications are key in identifying medicinal targets. In addition, such a strategy would be ideal for the preparation of PET imaging agents because mildly nucleophilic $^{18}\text{F}^-$ reagents, especially Cs^{18}F , can be readily prepared.

Grushin's elegant mechanistic studies of isolated $[\text{L}_n\text{M}(\text{Ar})(\text{F})]$ complexes (L is a ligand and M

is Pd or Rh) have demonstrated that reductive elimination to form an Ar-F bond is extremely challenging (22–27). These experiments have shown that undesired reaction pathways involving supporting ligands and fluoride dominate the chemistry of these complexes. This is due to both the high barrier to Ar-F bond formation as well as favorable pathways involving ligand-based P-F or C-F bond formation. In addition, the accessibility of stable $[\text{L}_n\text{Pd}(\text{Ar})(\text{F})]_2$ dimers has been suggested to contribute to the difficulty in achieving the desired reductive elimination (28). These results have cast doubt on whether a catalytic cycle as depicted in Fig. 1 is viable. We note, however, that for the heavier halides the reductive elimination of ArX (X is Cl, Br, or I) from a Pd(II) intermediate is preceded (29). In addition, it was recently shown that the dimeric Pd complex $[(o\text{-tol})_3\text{PPd}(p\text{-NO}_2\text{C}_6\text{H}_4)(\text{F})]_2$ yielded 10% of *para*-fluoronitrobenzene upon heating in benzene in the presence of an excess of ligand **1** (28), a ligand initially developed in our laboratories for use in C-N bond-forming reactions (Fig. 2). Although it has been questioned whether this latter reaction proceeds via a conventional reductive elimination (30), we were intrigued by the possibility that biaryl monophosphine ligands could promote this type of difficult reductive elimination to form Ar-F bonds.

Herein, we report the preparation of a well-characterized Pd(II) complex that undergoes reductive elimination producing an aryl fluoride. On the basis of this result, we have developed a palladium-catalyzed method for the preparation of aryl fluorides from aryl triflates using CsF that proceeds with high functional group tolerance under mild reaction conditions.

Ar-F reductive elimination from a Pd(II) complex. Recently, we reported a monophosphine ligand, BrettPhos (**2**), for use in aryl amination reactions (31) (Fig. 2). Nuclear magnetic resonance (NMR) and crystallographic studies of $[\text{2-Pd}(\text{Ar})(\text{X})]$ (X is Cl or Br) complexes revealed that they were monomeric both in solution and in the solid state. We decided to prepare analogous $[\text{2-Pd}(\text{Ar})(\text{F})]$ complexes in order to determine whether they were also monomeric and to see whether **2** could be useful as a ligand in promoting reductive elimination to form Ar-F bonds (32). We found that these targets were best accessed by transmetalation of the $[\text{2-Pd}(\text{Ar})(\text{Br})]$ complexes with AgF at room temperature

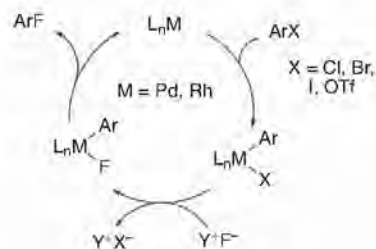


Fig. 1. Metal-catalyzed aryl fluorination.

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in dichloromethane (Fig. 3). The isolated $[2\cdot\text{PdAr}(\text{F})]$ complexes exhibit a characteristic doublet in ^{31}P and ^{19}F NMR spectra with a coupling constant $^2J_{\text{PF}}$ of ~ 175 Hz, depending on the aryl group. The x-ray structure of **4** (Ar = 2-methyl-4-trifluoromethylphenyl) confirmed the monomeric nature of the complex (Fig. 4).

We next examined the thermolysis of **4** and **5** at 100°C in toluene and found that reductive elimination to form **6** and **7** occurs in yields of 15% and 25%, respectively (Fig. 3), which demonstrates that Ar-F bond formation is possible with use of these complexes. The yields in these reactions could be increased to 45% of **6** and 55% of **7** if the reductive eliminations were conducted in the presence of an excess of the corresponding aryl bromide (33, 34). In these cases, the ^{31}P NMR spectra of the reaction mixtures showed that the oxidative-addition complexes $[2\cdot\text{PdAr}(\text{Br})]$ were formed as the only phosphorous-containing products, suggesting $\text{LPd}(\text{O})$ is formed along with the ArF product.

Having demonstrated that oxidative addition, halide exchange (transmetalation), and reductive elimination were all possible, we next examined the catalytic conversion of ArBr **8** to ArF **7**. Upon treatment of **8** with AgF (1.5 equivalents) and 10 mole percent (mol%) each of **2** and $[(\text{COD})\text{Pd}(\text{CH}_2\text{TMS})_2]$ (COD is 1,5-cyclooctadiene) (**35**) at 110°C for 18 hours, a 52% yield of **7** was observed, which was increased to 74% after optimization of the reaction conditions (Fig. 5). No product was detected in control experiments that omitted **2** and/or the Pd precatalyst. This result demonstrates that Pd complexes supported by BrettPhos can catalyze the conversion of an aryl bromide to an aryl fluoride. However, the scope of aryl bromides that could be effectively transformed is to date limited to electron-poor substrates bearing an ortho substituent, in line with the observation that no reductive elimination took place from $[2\cdot\text{PdAr}(\text{F})]$ complexes with Ar being 3,5-dimethylphenyl or 4-*n*-butylphenyl.

Efficient catalysis with aryl triflates. Concurrently, we also examined the use of aryl triflates as substrates. Although initial reactions of the triflate of 1-naphthol (**9**) provided only a trace of product **10**, the use of CsF in place of AgF as the fluoride source gave **10** in 30% yield (Fig. 6). In addition, 5% of naphthalene (**11**) was also observed. We also found that the read-

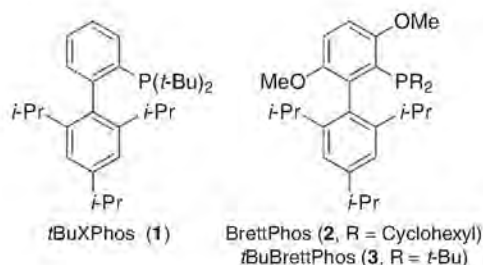


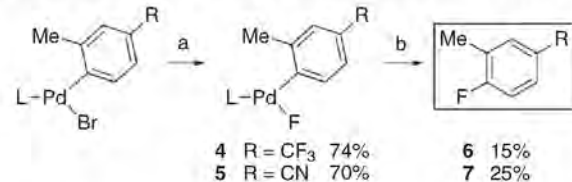
Fig. 2. Ligands for the successful reductive elimination of Ar-F.

ily prepared and more stable $[(\text{cinnyl})\text{PdCl}]_2$ could be used as the Pd precatalyst with a similar outcome. Overall, this result is important because it demonstrates that the fluorination can be carried out without needing a stoichiometric quantity of a noble metal component while still using a nucleophilic fluoride source.

In order to optimize the Ag-free reaction, a broad range of ligands were examined; under these conditions (Fig. 6), only ligands closely related to **2** provided more than a trace amount

of **10** (36, 37). Best results were obtained with use of *t*BuBrettPhos (**3**) (Fig. 2) as ligand; a 71% yield of **10** was realized, with only 1% of reduction product **11** observed. Further optimization of the reaction conditions increased the yield of **10** to 79%. Because the reaction proved to be sensitive to water (38), commercially obtained CsF was dried at 200°C under vacuum overnight and handled in a nitrogen-filled glovebox. Replacing CsF with spray-dried KF afforded **10** in 52% yield. No reaction was observed in the

Fig. 3. Preparation of and reductive elimination from $[2\cdot\text{PdAr}(\text{F})]$ complexes.



L = **2**. ^a 5 equiv. AgF, CH_2Cl_2 , 25°C , exclusion of light, 12 to 24 h.

^b toluene, 100°C , 2 h, yields determined by ^{19}F NMR spectroscopy.

Fig. 4. X-ray structure of complex **4** [ORTEP (www.ornl.gov/sci/ortep/ortep.html) drawing at 50% probability, hydrogen atoms omitted for clarity].



Fig. 5. Catalytic conversion of aryl bromide **8** to aryl fluoride **7**.

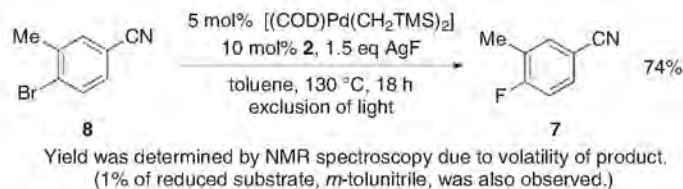
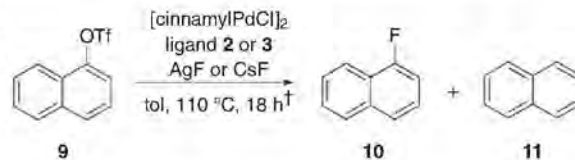


Fig. 6. Optimization of aryl triflate fluorination. Conversion and yield were determined by GC.



Pd (mol%)*	Ligand (mol%)	F source (eq)	Conversion	10	11
10	2 (10)	AgF (1.5)	†	trace	†
10	2 (10)	CsF (1.5)	90%	30%	5%
10	3 (10)	CsF (1.5)	100%	71%	1%
2	3 (3)	CsF (2.0)	100%	79%	1%

* mol% of palladium equivalents ("Pd"). † time not optimized,

‡ not determined

absence of the catalyst, ruling out both classic nucleophilic aromatic substitution (S_NAr) and aryne mechanisms (39).

We realized that for some applications, including PET, it was necessary to have a faster process. We found that the conversion of **9** to **10**, using 5 mol% [(COD)Pd(CH₂TMS)₂] as precatalyst, 10 mol% of **3** as supporting ligand, and 3 equivalents of CsF, was complete in 2.5 hours in toluene at 110 °C, yielding 80% of **10**. Increasing

the amount of CsF to 6 equivalents and adding 30 mol% of the solubilizing agent poly(ethylene glycol) dimethyl ether (Me₂PEG) led to full conversion in less than 30 min, albeit in yield of 71%. Similar rates of reaction could be achieved by using [(cinnamyl)PdCl]₂; with 5 mol% of this palladium source and 15% ligand, the reaction proceeds to completion in ≤2 hours in 79% yield (NMR). We are in the process of identifying conditions to achieve faster conversion of the sub-

strate without diminishing the yield, as required for PET applications.

As can be seen in Fig. 7, the fluorination of aryl triflates has substantial scope. Simple aromatic substrates, such as *ortho*-biphenyl triflate, react rapidly to provide aryl fluorides in high yield. Hindered substrates such as 4-acetyl-2,6-dimethylphenyl triflate are also efficiently converted to product (**13**). Electron-deficient arenes can be efficiently transformed by using only 2 mol% of catalyst (**14**, **18**, and **19**). Important from a practical standpoint, a variety of heterocyclic substrates can also be successfully fluorinated by using these conditions. Flavones (**17**), indoles (**21**), and quinolines (**22** to **24**) were all converted in good yield. More complex aryl triflates derived from fluorescein (**20**) and quinine (**25**) could also be effectively converted to their fluorinated analogs, demonstrating that this method can be used in the preparation of pharmaceutically relevant compounds. In some cases, product formed in high yield at 80 °C (**14**, **17**, and **24**). On a 10 mmol scale, butyl 4-fluorobenzoate **14** was prepared at 80 °C with no observable formation of reduced by-product (in general, 2% or less reduction product was observed across the range of substrates screened).

Many functional groups are tolerated, an exception being Lewis basic groups such as amines or carbonyls in the *ortho* position of the aryl triflate. No reaction takes place in these instances, presumably because the basic group coordinates the Pd center, possibly preventing transmetalation. As in the Pd-catalyzed formation of Ar-O bonds, the transformation of electron-rich substrates was more challenging. We found that good yields were obtained at higher temperatures (130 °C).

Formation of regioisomers. Unexpectedly, regioisomeric products were formed in a few cases (Figs. 8 and 9). Because control experiments did not yield any product in the absence of catalyst, we believe that isomer formation is also a palladium-catalyzed process. Investigating a series of tolyl (**26** to **28**) and anisole (**29** to **31**) triflates, we found that for substrates **26**, **27**, and **29** the observed selectivities are quite distinct from those reported for a benzyne process (39) (Fig. 8). Experiments with 2,6-dideuterated anisole triflate **31** showed a reduced rate of formation of the undesired regioisomer, whereas the rate of formation of the desired product remained largely unchanged, leading to a 2.5-fold increase in selectivity in comparison to the reaction with unlabeled **31**. Thus, at least for this substrate, we conclude that two competing pathways are involved; it is evident that hydrogen abstraction is the rate-limiting or the first irreversible step in regioisomer formation and that little or none of the desired isomer is formed from the path that finally leads to the regioisomer.

Although we do not have a complete mechanistic understanding of the pathway leading to the regioisomers, we have found that the product ratio

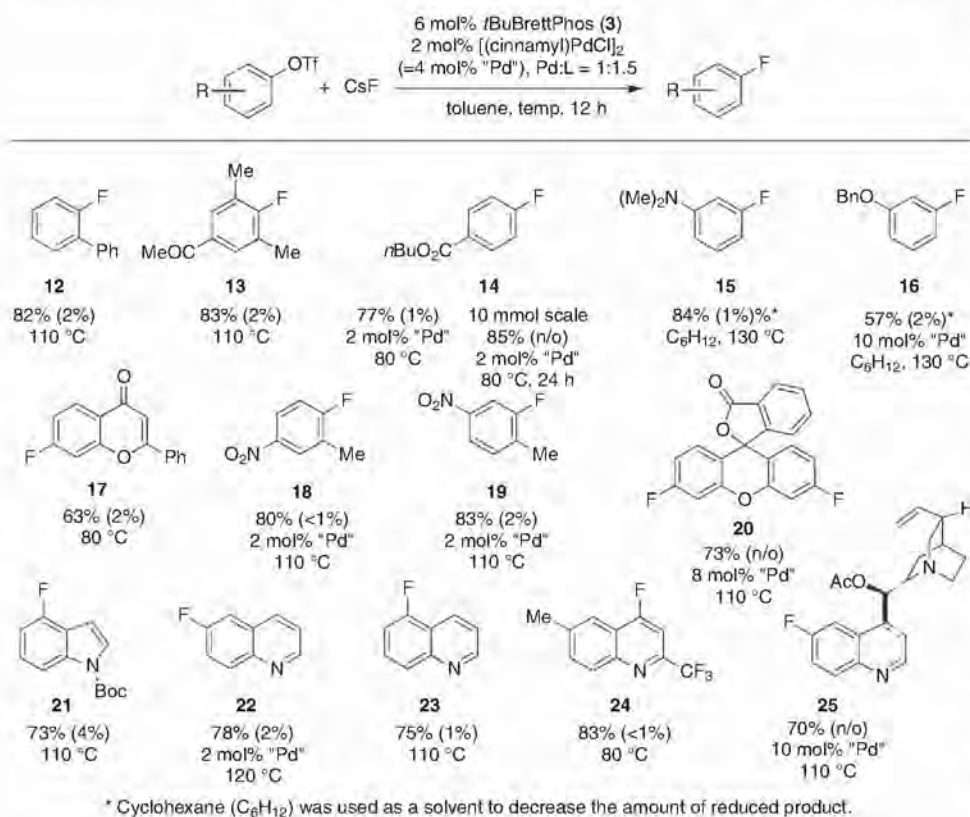


Fig. 7. Fluorination of aryl triflates. Isolated yields are an average of at least two independent reactions. Values in parentheses denote the amount of reduced starting material based on the isolated product yield (n/o indicates not observed). In cases with different palladium loading, the ligand amount was adjusted accordingly ("Pd":L = 1:1.5). Quotation marks around Pd symbols indicate the amount of Pd, not of the Pd dimer.

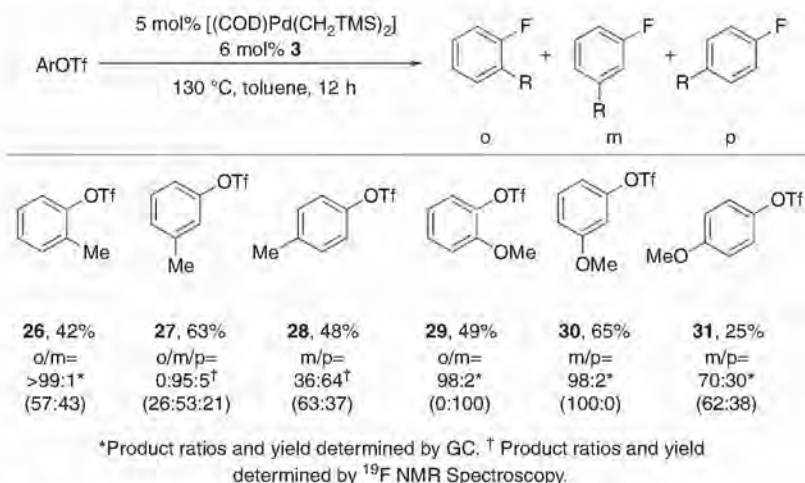
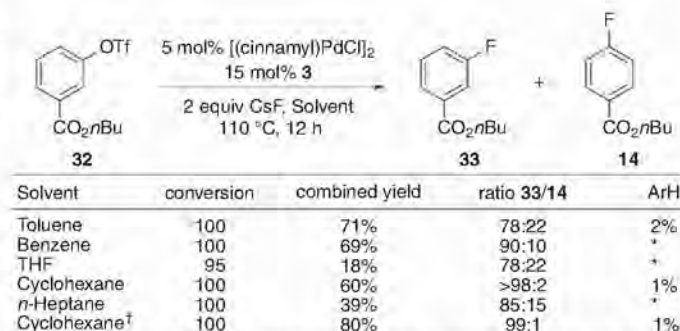


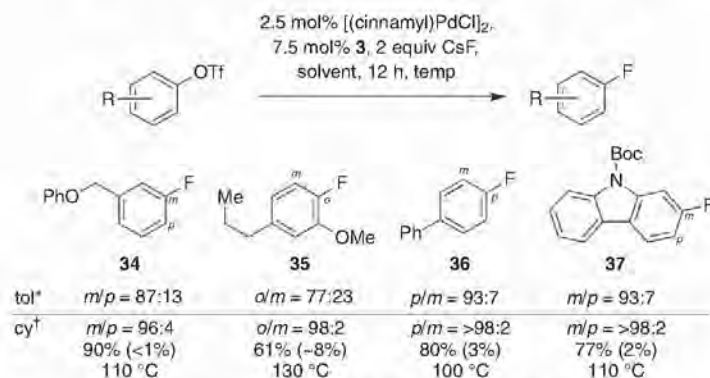
Fig. 8. Regioisomers in tolyl and anisole fluorination. Chemical yields are given as the sum of ArF products. Traces of reduction products were also observed. Ratios are compared with those of a reported fluorination of bromoaryls that proceeds via a benzyne intermediate (in parentheses) (39).

Fig. 9. Solvent screen and fluorination of triflates that gave regioisomers. Unless otherwise noted, yields and ratios determined by GC and ^{19}F NMR.



* Yield not determined. † Optimized condition 100 °C, isolated yield.

Fig. 10. Use of cyclohexane as solvent to suppress formation of regioisomers. Desired isomer is shown. Product ratios are for regioisomeric aryl fluorides as indicated. Isolated yields are for the major isomer, with values in parentheses denoting the amount of reduced starting material based on the isolated product yield.



* 2.5–5 mol% [(cinnamyl)PdCl]₂, 7.5–15 mol% 3, solvent = toluene.

† solvent = cyclohexane.

can be strongly affected by solvent polarity; the desired pathway is favored in highly apolar media. Examination of a number of solvents for the conversion of **32** to **33** revealed that the formation of the undesired isomer **14** is almost completely suppressed with use of cyclohexane (Fig. 9). This trend appears to be general; in most instances in which the undesired regioisomer was observed with use of toluene, switching to cyclohexane afforded almost exclusively the desired product. For example, fluorinated aryls **33** to **37** could be prepared with greater than 95:5 selectivity favoring the desired isomer (Fig. 10). This modification provides a highly practical means to minimize formation of regioisomeric by-products.

Outlook. Starting from the observation of the reductive elimination of ArF from a [2-PdAr(F)] complex, we have developed a metal-catalyzed direct conversion of aryl bromides and aryl triflates into the corresponding aryl fluorides using simple fluoride sources such as AgF and CsF. In particular, the transformation of aryl triflates exhibits a wide substrate scope and tolerates a number of functional groups, allowing for the introduction of fluorine atoms into highly functionalized organic molecules. Key to these findings was the use of the sterically demanding, electron-rich biaryl monophosphine *t*BuBrettPhos **3** as the supporting ligand. We believe that this ligand not only promotes reductive elimination of the Ar-F bond because of its large size but also prevents the formation of dimeric [LPdAr(F)]₂ complexes. At present, both of these factors appear to be critical in the successful catalytic reaction. Although some limitations remain with regard to substrate scope and reaction conditions,

we expect this method to be applicable to the preparation of biologically active and radio-labeled aryl fluorides.

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- The lower yield in the absence of added aryl bromide suggests that the 2-Pd(0) complex that results from reductive elimination further reacts with remaining [2-PdAr(F)] complex. Increased product yields have previously been observed in the reductive elimination of C-S bonds from Pd(II) centers when Pd⁰ scavengers (exogenous ligand) have been added to the reaction. See (34).
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- After this paper was submitted, we found that the closely related hetero-biaryl ligand 5-(di-*tert*-butylphosphino)-1-(1,3,5-triphenyl-1H-pyrazol-4-yl)-1H-pyrazole (Bippypfos) reported by Singer and co-workers [see (37) and citations therein] can also provide catalysts with moderate levels of activity for fluorination. For example, with use of 10 mol% of this ligand and 5 mol% [(cinnamyl)ClPd]₂, a 52% yield of **10** along with 11% reduction product was observed after heating for 12 hours at 150 °C in toluene.
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- We followed the reaction of **9** to **10** by gas chromatography (GC) and found that, after a brief initial period in which about 20% of **9** was consumed, **10** began to form. By adding 20 mol% water, we observed that the initial loss of material increased to 60%. This result indicates that one molecule of water consumes two molecules of **9** under the reaction conditions. Nevertheless, the reaction proceeded to give 40% **10**. We believe that the initial loss of mass balance is due to formation of biaryl ether: Presumably, adventitious water results in the formation of phenol, which further reacts with a second molecule of ArOTf in a Pd-catalyzed process.
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- We thank the NIH for financial support of this project (grant GM46059) and Merck, Nippon Chemical, Boehringer Ingelheim, and BASF for gifts of chemicals and additional funds. M.S. thanks the Singapore-MIT Alliance for a graduate fellowship. J.G.-F. thanks the Spanish Ministerio de Educación y Ciencia for a postdoctoral fellowship. T.K. thanks the Alexander von Humboldt Foundation for a Feodor Lynen postdoctoral fellowship. The Varian NMR instrument used was supported by the NSF (grants CHE 9808061 and DBI 9729592). We also thank P. Müller for obtaining the crystal structure of **4**. Cambridge Crystallographic Data Centre (CCDC) 741377 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif. A patent application has been filed by MIT covering portions of this work with S.L.B., D.A.W., M.S., and G.T. as co-inventors.

Supporting Online Material

www.sciencemag.org/cgi/content/full/1178239/DC1
Materials and Methods
Figs. S1 to S60
Table S1 to S5
References

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High-Detectivity Polymer Photodetectors with Spectral Response from 300 nm to 1450 nm

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Sensing from the ultraviolet-visible to the infrared is critical for a variety of industrial and scientific applications. Today, gallium nitride-, silicon-, and indium gallium arsenide-based detectors are used for different sub-bands within the ultraviolet to near-infrared wavelength range. We demonstrate polymer photodetectors with broad spectral response (300 to 1450 nanometers) fabricated by using a small-band-gap semiconducting polymer blended with a fullerene derivative. Operating at room temperature, the polymer photodetectors exhibit detectivities greater than 10^{12} cm Hz^{1/2}/W and a linear dynamic range over 100 decibels. The self-assembled nanomorphology and device architecture result in high photodetectivity over this wide spectral range and reduce the dark current (and noise) to values well below dark currents obtained in narrow-band photodetectors made with inorganic semiconductors.

Sensing from the ultraviolet (UV)-visible to the infrared is critical for a variety of industrial and scientific applications, including image sensing, communications, environmental monitoring, remote control, day- and night-time surveillance, and chemical/biological sensing (1–4). Today, separate sensors or materials are required for different sub-bands within the UV to near-infrared (NIR) wavelength (λ) range. In general, GaN-, Si-, and InGaAs-based detectors are used for the three important sub-bands, 0.25 μ m to 0.4 μ m (UV), 0.45 μ m to 0.8 μ m (visible) and 0.9 μ m to 1.7 μ m (NIR), respectively. The detectivities of silicon photodetectors are $\sim 4 \times 10^{12}$ Jones (1 Jones = 1 cm Hz^{1/2}/W). The typical detectivities of InGaAs photodetectors are greater than 10^{12} Jones when cooled to 4.2 K. It would be advantageous to have a low-cost multicolor photodetector system with high quantum efficiency, high sensitivity, and high speed over the broad spectral range from the UV to the NIR and which does not require cooling to obtain high detectivity.

Colloidal inorganic semiconductor quantum dots (PbS) were used to fabricate NIR photodetectors onto gold interdigitated electrodes (5, 6). These NIR photodetectors showed photoconductive gain and photoresponse out to 1450 nm. However, the quantum dot NIR photodetectors were fabricated using the “in-plane” structure (two electrodes and the PbS quantum dot semiconductor all in one plane) with electrode spacing > 5 μ m. As a result, the required driving voltage is too high (> 40 V) to be used with any commercially available thin film transistors (TFTs) (6).

These limitations substantially restrict the application of inorganic photodetectors in day- and night-time surveillance and chemical/biological sensing where high-speed and low-power photodetectors are desired.

After the initial discovery of ultrafast photoinduced electron transfer from semiconducting polymers to fullerenes (7), polymer photodetectors (PPDs) with fast temporal response and high sensitivity were reported with spectral response from 400 nm to 900 nm (8–12). However, there is no report on PPDs with photoresponse spanning the full range from the UV-visible to the NIR. We have successfully demonstrated PPDs with photoresponsivity from the UV to 1450 nm, fabricated by spin-casting the small-band-gap conjugated polymer, poly(5,7-bis(4-decanyl-2-thienyl)-thieno(3,4-*b*)diathiazole-thiophene-2,5) (PDDTT), blended with (6,6)-phenyl-C₆₁-butyric acid methyl ester (PC₆₀BM).

The molecular structures of PDDTT and PC₆₀BM are shown in Fig. 1A. PDDTT was synthesized using the Stille coupling reaction (13–15). Figure 1B shows the normalized UV-visible absorption spectra of thin films of pristine PDDTT, pristine PC₆₀BM, and PDDTT:PC₆₀BM composites. The inset shows the absorption spectra in the short-wavelength range from 300 nm to 500 nm. Pristine PDDTT thin films exhibit two absorption peaks, at ~ 480 nm and ~ 860 nm. The onset of the PDDTT absorption is at $\lambda = 1450$ nm, in good agreement with the calculated theoretical value obtained from geometry-optimized density functional calculations [see Supporting Online Material (SOM)] (16–18). The onset wavelength at 1450 nm is the result of the small single-chain energy gap of PDDTT (~ 0.8 eV), which is sensitive to an increase (or decrease) in conjugation length (19, 20). The addition of 50% w/w of PC₆₀BM does not substantially alter the absorption properties of PDDTT; the new spectral feature that appears between 350 nm and 500 nm in the spectrum of

the PDDTT:PC₆₀BM composites originates from PC₆₀BM.

The energy levels [highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO)] of PDDTT and PC₆₀BM were determined by cyclic voltammetry. The results are shown in Fig. 1C along with the work functions of indium tin oxide (ITO) and aluminum (Al). Figure 1C also shows the energy diagrams for poly[3-(vinylcarbazole)] (PVK), C₆₀, polystyrene-N,N-diphenyl-N,N-bis(4-n-butylphenyl)-(1,10-biphenyl)-4,4-diamine-perfluorocyclobutane (PS-TPD-PFCB) and the work function of poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS). (The molecular structures of PVK, C₆₀, and PS-TPD-PFCB are shown in the SOM.) Based on the energy-level diagrams shown in Fig. 1C, charge-separated carriers can be efficiently generated by photo-induced electron transfer and subsequently transported via the bulk heterojunction nanomorphology to opposite electrodes. Any barriers to charge collection at the electrodes are small as a result of the small energy differences at the PDDTT-ITO interface and at the PC₆₀BM-Al interface.

The short-circuit current observed from ITO/PEDOT/PDDTT:PC₆₀BM/Al devices (Fig. 2A) is ~ 200 times as high as that from ITO/PEDOT/PDDTT/Al devices, indicating that mobile carriers are photogenerated by ultrafast photoinduced electron transfer at a PDDTT:PC₆₀BM heterojunction (7, 21). Time-resolved photoinduced absorption and transient photoconductivity were carried out to verify the ultrafast photoinduced charge transfer and to verify the generation of long-lived mobile carriers (see the results in the SOM). We note that because of the high absorption coefficient over this broad absorption spectral region, PDDTT is a promising semiconducting polymer for use in bulk heterojunction photovoltaic cells. The absorption spectrum of PDDTT:PC₆₀BM covers nearly the entire solar emission spectrum.

To achieve high sensitivity, we fabricated the polymer photodetector using phase-separated bulk heterojunction blends. The PDDTT:PC₆₀BM bulk heterojunction active layer (Fig. 2A) forms interpenetrating bicontinuous donor and acceptor networks. Figure 2A shows the device architecture. The composition of PEDOT:PSS (as formulated for use in PPDs) and the details of the device fabrication are given in the SOM. A tungsten lamp was used as the light source to measure the PPDs' photoresponsivity. Figure 2B shows the current-voltage (*I*-*V*) characteristics measured in the dark and under illumination with $\lambda = 800$ nm with intensity of 0.22 mW/cm². The photodetector diode exhibits a rectification ratio of $\sim 10^3$ (at ± 1 V bias) in the dark. To obtain the responsivity (*R* in A/W), the ratio of photocurrent to incident-light intensity must be measured

$$R = J_{ph}/L_{light} \quad (1)$$

where J_{ph} is the photocurrent and L_{light} is the incident light intensity. Thus, we measured the

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Fig. 1. (A) Molecular structures of PDDTT and PC₆₀BM. (B) Absorption spectra of thin films: pristine PDDTT, pristine PC₆₀BM, and PDDTT:PC₆₀BM bulk heterojunction composites. Inset shows the absorption spectra from 300 to 500 nm. (C) Energy-level diagrams of PDDTT, PC₆₀BM, PVK, PS-TPD-PFCB, C₆₀, ITO, PEDOT, and Al.

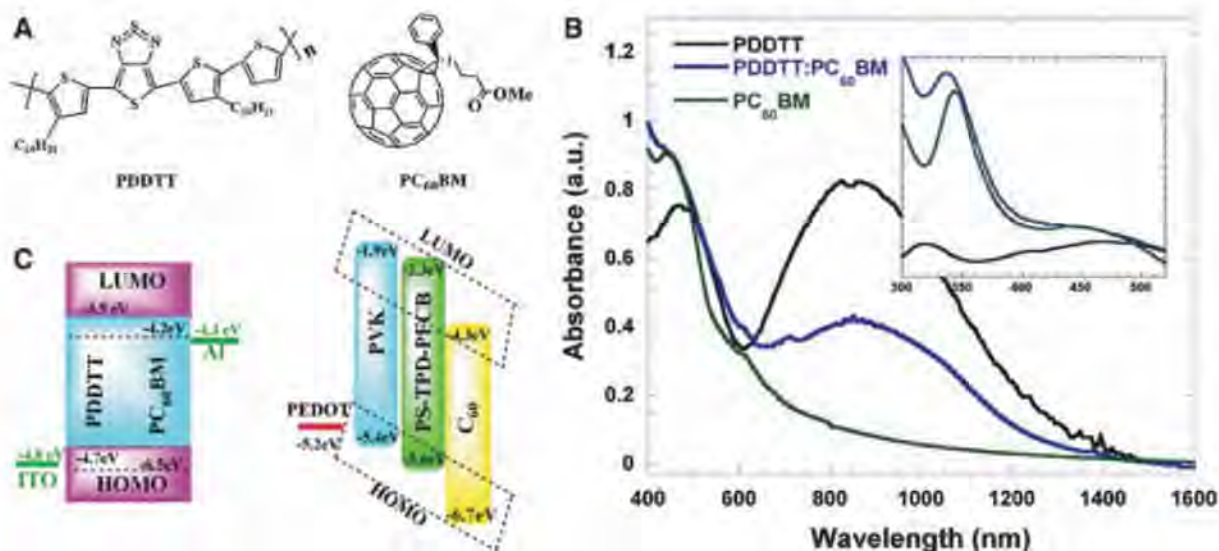
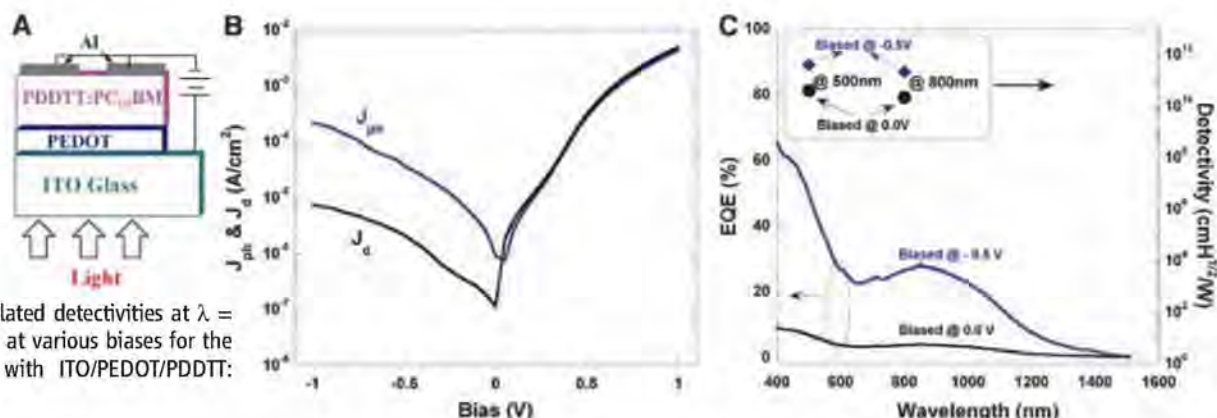


Fig. 2. (A) Schematic layout of the ITO/PEDOT/PDDTT:PC₆₀BM/Al photodetector on glass substrate. (B) Current-voltage (*I*-*V*) characteristics of polymer photodetectors measured in the dark and under illumination with $\lambda = 800$ nm. (C) EQE versus wavelength and calculated detectivities at $\lambda = 500$ nm and $\lambda = 800$ nm at various biases for the polymer photodetectors with ITO/PEDOT/PDDTT:PC₆₀BM/Al architecture.



external quantum efficiency (EQE) under short-circuit conditions and under reverse bias using the lock-in amplifier technique. The data are presented in Fig. 2C. The similar profiles of absorption and EQE spectra of PDDTT:PC₆₀BM (Figs. 1B and 2C) demonstrate that photons absorbed by PDDTT in the NIR do indeed contribute to the photocurrent. At $\lambda = 800$ nm, the EQE is 26% electron per photon. Accordingly, R is calculated using Eq. 1 to be 0.17 A/W.

The photodetector figure of merit is the noise equivalent power (NEP), i.e., the minimum impinging optical power that a detector can distinguish from the noise.

$$NEP = (A\Delta f)^{1/2}/D^* \quad (2)$$

where A is the effective area of the detector in cm², Δf is the electrical bandwidth in Hz, and D^* is the detectivity measured in units of Jones. D^* is given by the following

$$D^* = (A\Delta f)^{1/2}R/i_n \quad (3)$$

where R the responsivity in A/W measured under the same conditions as the noise current i_n (in amperes).

There are three contributions to the noise that limit D^* (22, 23): shot noise from dark current,

Johnson noise, and thermal fluctuation “flicker” noise. If, as expected, the shot noise from the dark current is the major contribution, the detectivity can be expressed as

$$D^* = R/(2qJ_d)^{1/2} = (J_{ph}/L_{light})/(2qJ_d)^{1/2} \quad (4)$$

where q is the absolute value of electron charge (1.6×10^{-19} Coulombs) and J_d is the dark current. Detectivities were calculated (based on the measured photocurrent, dark current, and incident light intensity) using Eq. 4 at $\lambda = 500$ nm and $\lambda = 800$ nm for the PPDs with the ITO/PEDOT/PDDTT:PC₆₀BM/Al structure.

At zero bias, the calculated detectivities are $D^* = 3.9 \times 10^{10}$ Jones and 2.1×10^{10} Jones for PPDs under the illumination at 500 nm with light intensity of 0.28 mW/cm² and 800 nm with light intensity of 0.22 mW/cm², respectively. With a bias at -500 mV, $D^* = 3.9 \times 10^{10}$ Jones and 2.1×10^{10} Jones for illumination at 500 nm and 800 nm, respectively.

As shown below, these modest detectivities are limited by the high dark current. In the bulk heterojunction blend, the dark current is determined by the energy difference, E_{PF} , between the HOMO (top of the valence or π -band) of PDDTT and the LUMO of PC₆₀BM. The dark current is given by the diode equation:

$$J_{\text{dark}} = J_0 \exp(eV/nkT) \quad (5)$$

where J_0 is the dark saturation current that is dependent on E_{PF} , V is the applied voltage across photodetector, e is absolute value of electron charge, k is Boltzmann’s constant, T is absolute temperature (K), and n is the ideality factor.

To minimize the dark current, we fabricated various polymer photodetectors with different multilayer structures. The general concept is to create blocking electrodes that suppress the thermally generated dark current. Polymer photodetectors with the following structures were characterized in detail:

- (i) PPD1: ITO/PDDTT:PC₆₀BM/Al
- (ii) PPD2: ITO/PEDOT/PDDTT:PC₆₀BM/Al
- (iii) PPD3: ITO/PEDOT/PDDTT:PC₆₀BM/C₆₀/Al
- (iv) PPD4: ITO/PEDOT/PVK/PDDTT:PC₆₀BM/C₆₀/Al
- (v) PPD5: ITO/PEDOT/PS-TPD-PFCB/PDDTT:PC₆₀BM/C₆₀/Al

Atomic force microscopy images clearly indicated that the film quality of PDDTT:PC₆₀BM directly on top of ITO was poor. Film quality of PDDTT:PC₆₀BM on top of a PEDOT planarization layer (cast onto top of ITO) was better (see SOM).

In Fig. 3A, we plot the measured photocurrent and dark current at -100 mV bias for each

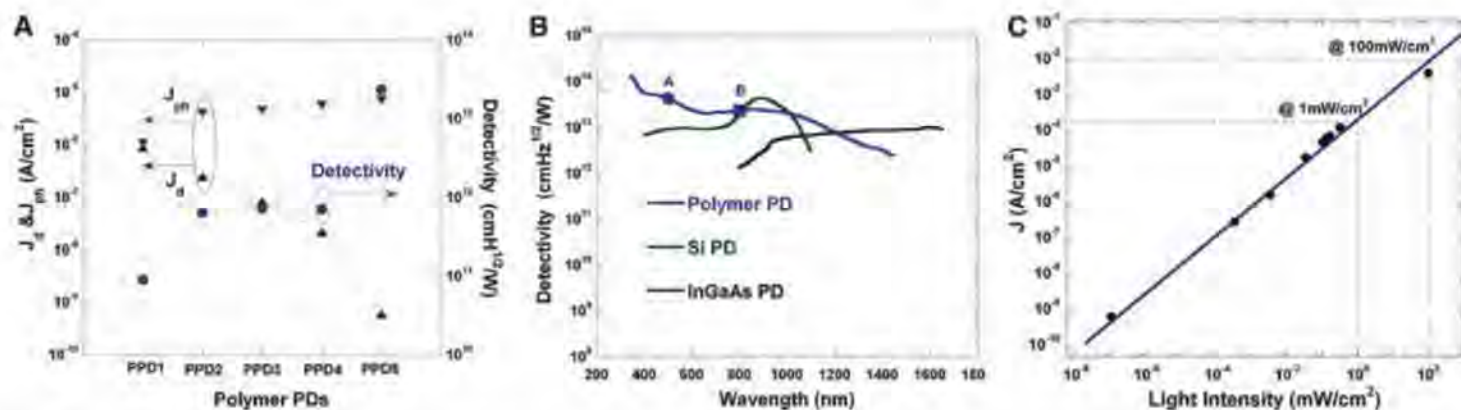


Fig. 3. (A) Photocurrent, dark current, and calculated detectivity at $\lambda = 800$ nm for each of the PPDs structures biased at -100 mV. (B) Detectivities of Si photodetector, InGaAs photodetector, and polymer photodetector versus wavelength. The high detectivities (10^{12} Jones) of the InGaAs photodetectors require cooling the devices to 4.2 K. The detectivities of the PPDs (ITO/PS-TPD-

PFCB/PDDTT:PC₆₀BM/C₆₀/Al) were calculated at $\lambda = 500$ nm (point A) and $\lambda = 800$ nm (point B) biased at -100 mV. The solid blue curve was obtained from the measured photoresponsivity data with absolute magnitude determined by points A and B. (C) LDR of the polymer photodetectors with ITO/PS-TPD-PFCB/PDDTT:PC₆₀BM/C₆₀/Al architecture.

of the PPD structures. Using these values, the detectivities at 800 nm were calculated using the equations given above with the assumption that the detectivity is limited by dark current. The best results (highest photocurrent, lowest dark current, and highest detectivity) were obtained with the PPD5 structure. As described above, a high dark current is expected from PPD1 and PPD2 devices because PDDTT is a narrow bandgap semiconducting polymer and E_{PF} is relatively small. In PPD3 and PPD4, a thin layer of C₆₀ blocks photogenerated holes from moving into the Al cathode and a thin layer of PVK blocks photogenerated electrons from moving into the ITO anode. As a result, higher photocurrents and lower dark currents were observed. Even better results were obtained (PPD5) by replacing the nonconjugated PVK, with the high-conductivity, cross-linkable, low-HOMO, hole-transporting polymer (electron blocking) PS-TPD-PFCB (24, 25). Figure 3A also shows the calculated detectivities at -100 mV bias for each of the PPDs when illuminated at 800 nm with a light intensity of 0.22 mW/cm². The results shown in Fig. 3A clearly demonstrate that achieving high detectivity requires not only high photoresponsivity (high photocurrent) but also low noise (low dark current).

In Fig. 3B, we compare the detectivities of PPDs with detectivities of Si and InGaAs photodetectors. As in Fig. 3A, the detectivities of PPD5 were calculated at 500 nm (4.2×10^{13} Jones) and 800 nm (2.3×10^{13} Jones) using the equations given above, with the assumption that the detectivity is limited by dark current. By combining the calculated detectivities at 800 nm with the photoresponsivity data, the PPDs' detectivity values were obtained over the entire spectral range (Fig. 3B). Operating at room temperature, the optimized PPDs exhibited spectral response from 300 nm to 1450 nm, with detectivity greater than 10^{13} Jones at wavelengths from 300 nm to 1150 nm and greater than 10^{12} Jones from 1150 nm to 1450 nm. The detectivity (Fig. 3B) of the PPDs is

comparable to or even better than those from Si and InGaAs photodetectors. Moreover, the PPD covers a significantly broader spectral range than Si or InGaAs photodetectors.

Another figure of merit for photodetectors is the linear dynamic range (LDR) or photo-sensitivity linearity (typically quoted in dB). LDR is given by

$$\text{LDR} = 20 \log(J_{ph}^*/J_d) \quad (6)$$

where J_{ph}^* is the photocurrent, measured at light intensity of 1 mW/cm². Figure 3C shows the photocurrent versus the light intensity for PPD5. Under illumination at $\lambda = 800$ nm, the LDR for PPD5 is more than 100 dB, which is close to that of a Si photodetector (120 dB) and significantly higher than that obtained from InGaAs photodetectors (66 dB).

The results presented here demonstrate that the performance parameters of polymer photodetectors based on PDDTT are comparable to or even better than photodetectors fabricated from inorganic materials. The achievement of high-performance polymer photodetectors implies that semiconducting polymers can be used in a variety of possible sensor applications. The photoresponsivity and detectivity results open exciting opportunities for the creation of detectors with unusually wide spectral range and for the fabrication of high-resolution detector arrays for optical communications, chemical/biological sensing, and day- and night-time surveillance.

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Reversible Reactions of Ethylene with Distannynes Under Ambient Conditions

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Ethylene's cycloadditions to unsaturated hydrocarbons occupy well-established ground in classical organic chemistry. In contrast, its reactivity toward alkene and alkyne analogs of carbon's heavier-element congeners silicon, germanium, tin, or lead has been little explored. We show here that treatment of the distannynes $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ [$\text{Ar}^{\text{IPr}} = \text{C}_6\text{H}_3-2,6(\text{C}_6\text{H}_3-2,6\text{-iPr}_2)_2$, **1**] or $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ [$\text{Ar}^{\text{IPr}} = \text{C}_6\text{H}-2,6(\text{C}_6\text{H}_2-2,4,6\text{-iPr}_3)_2-3,5\text{-iPr}_2$, **2**] with ethylene under ambient conditions affords the cycloadducts $\text{Ar}^{\text{IPr}}_2\text{Sn}(\mu_2\text{-}\eta^1\text{-}\eta^1\text{-C}_2\text{H}_4)_2\text{SnAr}^{\text{IPr}}_2$ (**3**) or $\text{Ar}^{\text{IPr}}_2\text{Sn}(\mu_2\text{-}\eta^1\text{-}\eta^1\text{-C}_2\text{H}_4)_2\text{SnAr}^{\text{IPr}}_2$ (**4**) that were structurally and spectroscopically characterized. Ethylene incorporation in **3** and **4** involves tin-carbon σ bonding and is shown to be fully reversible under ambient conditions; hydrocarbon solutions of **3** or **4** revert to the distannynes **1** or **2** with ethylene elimination under reduced pressure or upon standing at $\sim 25^\circ\text{C}$. Variable-temperature proton nuclear magnetic resonance studies showed that the enthalpies of reaction were near -48 (**3**) and -27 (**4**) kilojoules per mole.

Cyclization processes involving olefins or alkynes are an exceedingly important reaction class in organic chemistry (1). The simplest reactions are those in which two π -bonded units combine to give two σ bonds within a four-membered ring (a "2+2" reaction). Such processes are usually symmetry forbidden on the basis of the Woodward-Hoffman rules (2). In contrast, the isolation of stable, heavier-element (Si, Ge, Sn, and Pb) analogs of alkenes (3, 4) and alkynes (5, 6) and the investigation of their properties has shown that they are highly reactive and can undergo cyclization reactions under mild conditions (7–11). A major reason for their enhanced reactivity is that their bonding and electronic structure differs considerably from their lighter carbon analogs (6). In effect, the altered shapes and lower energy separation of their frontier orbitals facilitate more rapid reactions (see below). Nonetheless, essentially all of the cyclization reactions of the alkyne congeners and related heavier main-group molecules are irreversible (7–16). The only exception is the reaction of the stannylene $\text{Sn}\{\text{CH}(\text{SiMe}_3)_2\}_2$ (**3**) with a strained alkyne unit incorporated in the seven-membered ring 3,3,6,6-tetramethyl-1-thiocyclohept-4-yne, which affords a stannacyclopentene product (17). Ethylene or 2-butyne afford an interesting 1,4-cycloaddition to the cation $[\text{HC}\{\text{C}(\text{Me})\text{N}(\text{C}_6\text{H}_3-2,6\text{-iPr}_2)_2\}_2\text{AlEt}]^+$ between aluminum and the α carbon (18). However, olefin release requires the use of a base that coordinates to the metal that, as a result, prevents further reaction. We now show that ethylene is reversibly incorporated through cycloaddition to the tin-tin triple bond in the distannynes $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ [$\text{Ar}^{\text{IPr}} = \text{C}_6\text{H}_3-$

$2,6(\text{C}_6\text{H}_3-2,6\text{-iPr}_2)_2$, **1**, (19)] $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ [$\text{Ar}^{\text{IPr}} = \text{C}_6\text{H}-2,6(\text{C}_6\text{H}_2-2,4,6\text{-iPr}_3)_2-3,5\text{-iPr}_2$, **2**, (20)]. The reaction proceeds in toluene at or below room temperature under 1 atm to afford the cycloadducts $\text{Ar}^{\text{IPr}}_2\text{Sn}(\mu_2\text{-}\eta^1\text{-}\eta^1\text{-C}_2\text{H}_4)_2\text{SnAr}^{\text{IPr}}_2$ (**3**) and $\text{Ar}^{\text{IPr}}_2\text{Sn}(\mu_2\text{-}\eta^1\text{-}\eta^1\text{-C}_2\text{H}_4)_2\text{SnAr}^{\text{IPr}}_2$ (**4**) that were characterized by nuclear magnetic resonance (NMR) and ultraviolet-visible spectroscopy and by single crystal x-ray crystallographic analysis. In solution or under reduced pressure, **3** and **4** spontaneously retrocyclize to yield free ethylene and the distannynes **1** or **2**.

The bis(ethylene) complexes **3** and **4** were prepared [see supporting online material (SOM) text] by treating a toluene solution of **1** or **2** with ethylene gas under 1 atm at 25°C (**1**) or 0°C (**2**) (Fig. 1). The initially green solution of **1** at 25°C changed within 1 min to an amber solution of **3**. For the reaction of **2**, the color change to the amber solution of **4** was not complete until the

solution was stored overnight under ethylene in a $\sim 18^\circ\text{C}$ freezer. Concentration of the solutions of **3** and **4** under reduced pressure at $\sim 25^\circ\text{C}$ resulted in reversion to the initial green color from which **1** or **2** could be recovered unchanged. The bis(ethylene) complexes **3** and **4** were obtained as yellow plates by cooling concentrated toluene solutions to $\sim 18^\circ\text{C}$ for 24 hours.

The complex **3** crystallized as two structurally similar, but crystallographically independent molecules, whereas **4** crystallized as crystallographically unique molecular units (21). The structure of one of the crystallographically independent molecules of **3** is shown in Fig. 2, and it may be contrasted with that of $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ (**1**), which has a trans-bent CSnSnC core geometry in which $\text{Sn-Sn} = 2.6675(4)$ Å, $\text{Sn-C} = 2.191(3)$ Å, and the Sn-Sn-C bending angle is $125.24(7)^\circ$ (19). In **3**, however, the Ar^{IPr}_2 ligands are cis with respect to each other with $\text{Sn-Sn-C}(\text{Ar}')$ bending angles that average $163.2(1.2)^\circ$. The Sn-Sn distance is increased to an average of $2.886(6)$ Å, and the $\text{Sn-C}(\text{Ar}')$ bond lengths average $2.19(2)$ Å. The two CH_2CH_2 moieties are each bound to the $\text{Ar}^{\text{IPr}}_2\text{SnSnAr}^{\text{IPr}}_2$ unit on the opposite side of the Sn-Sn axis from the Ar^{IPr}_2 ligands. The carbon atoms in each of the C_2H_4 moieties are bound to different tin atoms to generate two fused Sn_2C_2 rings with a common tin-tin bonded side and an average dihedral angle of $\sim 97^\circ$ between the Sn_2C_2 ring planes; in other words, the compound has a 1,4-distannabicyclo[2.2.0]butane structure [a similar structural motif has been observed in a number of other group 14 element derivatives (7, 22–24)]. The average Sn-CH_2 distance is $2.19(2)$ Å, which is indistinguishable from the $\text{Sn-C}(\text{Ar}')$ distance. The key C-C bond length within the CH_2CH_2 units averages $1.54(5)$ Å. The overall structure thus features C-C , Sn-C , and Sn-Sn bond lengths in the $\{\text{C}(\text{ipso})\}_2\text{Sn}_2(\text{CH}_2\text{CH}_2)_2$ core array that are indicative of single bonding (25). The C-C ring distances, in particular, and the quasi tetrahedral geometries at their carbons are consistent with a distannacyclobutane formula-

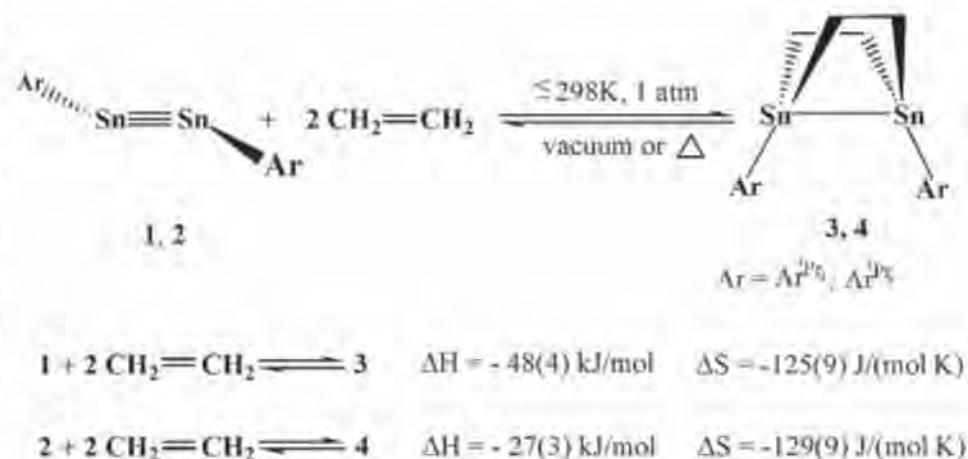
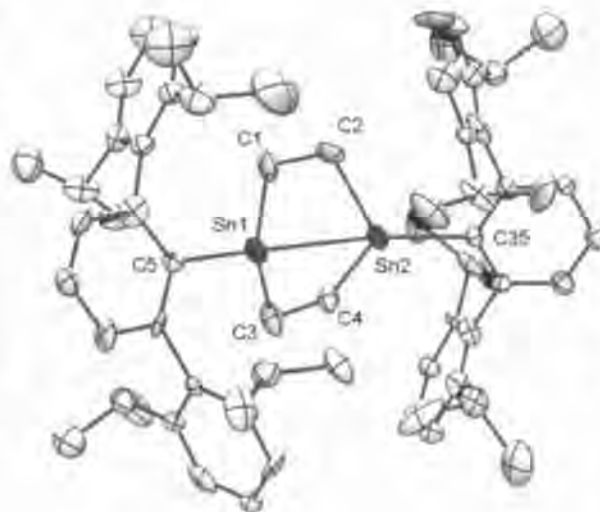


Fig. 1. Reversible binding of ethylene to ArSnSnAr [$\text{Ar} = \text{Ar}^{\text{IPr}}_2(\text{C}_6\text{H}_3-2,6(\text{C}_6\text{H}_3-2,6\text{-iPr}_2)_2)$ or $\text{Ar}^{\text{IPr}}_2(\text{C}_6\text{H}-2,6(\text{C}_6\text{H}_2-2,4,6\text{-iPr}_3)_2-3,5\text{-iPr}_2)$].

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Fig. 2. Thermal ellipsoid (30%) drawing of one of the crystallographically independent molecules of **3**. Hydrogen atoms are not shown. Selected average bond lengths (in angstroms) and angles (in degrees Celsius) for both molecules are as follows: Sn1-Sn2, 2.886(6) Å; C1-C2, 1.528(8) Å; C3-C4, 1.552(8) Å; Sn1-C5, 2.203(6) Å; Sn2-C35, 2.179(6) Å; Sn1-C1, 2.184(6) Å; Sn1-C3, 2.191(6) Å; Sn2-C2, 2.202(6) Å; Sn2-C4, 2.178(6) Å; C5-Sn1-Sn2, 162.4(1)°; C1-Sn1-C3, 100.6(2)°; C2-Sn2-C4, 98.6(3)°; C35-Sn2-Sn1, 164.0(1)°.



tion for the two core rings. The structural parameters of **4** closely resemble those of **3** (SOM text), and the complexed ethylenes also involve Sn-C and C-C distances consistent with single bonding.

The spectroscopic data for **3** and **4** support this picture. For example, the observed $^2J_{\text{SnH}}$ coupling for **3** of 46 Hz is within the known range for Sn-CH₂ moieties, and the ^1H NMR chemical shifts of the CH₂CH₂ hydrogens are in the alkane, rather than the alkene region (26–28). The ^{119}Sn NMR spectrum of **3** exhibits a singlet at 343 parts per million with $^1J_{119\text{Sn}-107\text{Sn}}$ coupling of 3130 Hz. The shift is downfield of the usual range for tetravalent organotin species (29), which may be due to the unusually strained geometry at the tin atoms. The electronic spectrum of **3** features an absorption at 366 nm and displays no trace of the absorptions due to **1** at 410 and 597 nm. The complex **4** displays similar spectral characteristics (SOM text) to those of **3**. However, crystals of **4** are less stable and can be stored only below -10°C .

Despite the apparently normal Sn-C and C-C single bond lengths, **3** and **4** readily dissociate both complexed -CH₂CH₂- units at or below room temperature, consistent with weak ethylene binding. A van't Hoff analysis of variable-temperature ^1H NMR spectra affords change in enthalpy of association (ΔH_{assn}) = $-48(4)$ kJ mol $^{-1}$ (**3**) and $-27(3)$ kJ mol $^{-1}$ (**4**) (figs. S1 and S2) and K values of 84(7) (**3**) and $7.9(7) \times 10^{-3}$ (**4**) at 298.16 K, confirming the weakness of the C-Sn cycloadduct bonds. Density functional theory calculations carried out on the model compounds PhSnSnPh and PhSn(μ_2 : η^1 : η^1 -C₂H₄)₂SnPh (table S3) afforded ΔH_{assn} = -133 kJ mol $^{-1}$. The higher calculated value is consistent with the much lower steric congestion in comparison to that in **3** or **4**. The apparent paradox of weak C-Sn bond strength in the face of normal C-C and Sn-C single bond lengths for **3** and **4** can be explained, at least in part, on the basis of the distorted geometry of the complexes. The environment at the tin centers in **3** and **4** is consistent with considerable strain: Instead of an approximately tetrahedral coordination, the inter-

atomic angles vary from $\sim 70^\circ$ to 160° in each complex [e.g., C(3)-Sn(1)-Sn(2) = $68.9(2)^\circ$ and C(5)-Sn(1)-Sn(2) = $161.3(2)^\circ$ in **4**]. Moreover, the very large Ar^{*ipr*} or Ar^{*ipr*} substituents are mutually cis, and there is a somewhat lengthened Sn-Sn bond of ~ 2.9 Å [compared with 2.8 Å in elemental tin (30)]. This arrangement may be contrasted with the short Sn-Sn bond and the preferred trans-geometry with Sn-Sn-C bending angles of $\sim 125^\circ$ observed in a distannynes **1** and **2**. Therefore, in the process of complex formation, **3** and **4** accumulate considerable potential energy. The energy gained by the formation of four Sn-C σ bonds is thus in approximate balance with the loss of two C-C π bonds and the accumulation of strain energy. Consequently, the equilibria **1** + 2C₂H₄ $\rightleftharpoons$ **3** and **2** + 2C₂H₄ $\rightleftharpoons$ **4** are strongly affected by the entropic $T\Delta S$ factor (where T is temperature and ΔS is change in entropy) in the expression for the Gibbs free energy, and relatively small physical changes can induce rapid and complete dissociation of the ethylenes. In effect, **3** and **4** are analogous to coiled springs [so-called “jack in the box” molecules (31)] that are primed to dissociate upon dissolution or when subject to reduced pressure.

In contrast to these results, the corresponding reaction of Ar^{*ipr*}GeGeAr^{*ipr*} [**5**, (32)] with ethylene yielded Ar^{*ipr*}Ge(μ_2 : η^1 : η^1 -C₂H₄)₂GeAr^{*ipr*} (**6**), whose structure (fig. S5, SOM text) is similar to those of **3** and **4** and that of the previously described (Me₃Si)₃CGe(μ_2 : η^1 : η^1 -C₂H₄)₂GeC(SiMe₃)₃ (**7**). The latter compound was obtained by reduction of the corresponding 1,2-dichloro-1,2-digermacyclobutane under ethylene, rather than by direct reaction with the digermene. It is an air-stable, colorless solid that decomposes above 200°C . Similarly for **6**, no retrocyclization could be observed up to 200°C . Possibly, the stronger Ge-C bonding stabilizes the core frameworks in these compounds.

The reaction of **1** or **2** with ethylene probably occurs via a pathway similar to that calculated (11) for the cyclization of a disilyne with olefins or alkynes in which the C-C bond interacts with

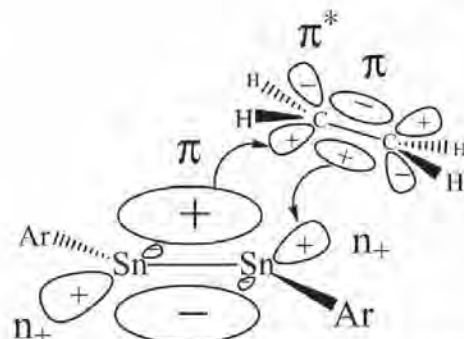


Fig. 3. Initial step of the addition of C₂H₄ to the ArSnSnAr species.

one of the group 14 element centers to form a three-membered SiC₂ ring species in the first instance (Fig. 3). Interaction with a second ethylene to the other tin atom may follow by a similar route with subsequent rearrangement to give **3** or **4**. However, the reaction of **1** or **2** with ethylene in 1:1 stoichiometries afforded **3** or **4** in reduced yield together with unreacted starting material. No 1:1 product could be detected by NMR spectroscopy. Neither **1** nor **2** react with propene under ambient conditions, though **1** (but not the more crowded **2**) reacts with norbornadiene at $\sim 25^\circ\text{C}$ to afford a 2:1 adduct (**7**, fig. S6, SOM text) analogous to **3** and **4**, which has a higher ΔH_{assn} of $-89(7)$ kJ mol $^{-1}$ (fig. S11), consistent with the strained nature of the olefin.

In summary, the distannynes **1** and **2** react reversibly with ethylene because of a rare combination of electronic, steric, and thermodynamic effects. It remains to be seen if suitable combinations of such factors can be induced in other main-group molecules to obtain reversible cyclizations.

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20. This distannylene was prepared in an analogous manner to that reported for **1** by a reduction of 1:1 mixture of SnCl_2 and $\text{LiAr}^{\text{Pr}}_3$ with KC_8 .
21. Crystal data for **3** and **4** were obtained at 90(2) K with the use of a Bruker APEX II CCD diffractometer and MoK α radiation ($\lambda = 0.71073$ Å). Crystal data are as follows: **3**; $a = 45.277(4)$ Å; $b = 17.7965(18)$ Å; $c = 16.3433(16)$ Å, $\beta = 100.538(2)^\circ$, monoclinic, Cc , $Z = 4$, R_1 for 33577 [data intensity $I > 2\sigma(I)$] data = 0.0645, wR_2 all data 0.1683; **4**; $a = 14.921(2)$ Å; $b = 15.866(2)$ Å; $c = 19.203(3)$ Å, $\alpha = 82.683(2)^\circ$, $\beta = 82.388(2)^\circ$, $\gamma = 71.207(2)^\circ$, triclinic, $P\bar{1}$, $Z = 2$, R_1 for 9210 [data intensity $I > 2\sigma(I)$] data = 0.0682, wR_2 (all data) = 0.1778.
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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5948/1668/DC1

SOM Text

Figs. S1 to S11

Tables S1 to S5

References

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Coordinationally Unsaturated Al^{3+} Centers as Binding Sites for Active Catalyst Phases of Platinum on $\gamma\text{-Al}_2\text{O}_3$

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In many heterogeneous catalysts, the interaction of metal particles with their oxide support can alter the electronic properties of the metal and can play a critical role in determining particle morphology and maintaining dispersion. We used a combination of ultrahigh magnetic field, solid-state magic-angle spinning nuclear magnetic resonance spectroscopy, and high-angle annular dark-field scanning transmission electron microscopy coupled with density functional theory calculations to reveal the nature of anchoring sites of a catalytically active phase of platinum on the surface of a $\gamma\text{-Al}_2\text{O}_3$ catalyst support material. The results obtained show that coordinatively unsaturated pentacoordinate Al^{3+} ($\text{Al}^{3+}_{\text{penta}}$) centers present on the (100) facets of the $\gamma\text{-Al}_2\text{O}_3$ surface are anchoring Pt. At low loadings, the active catalytic phase is atomically dispersed on the support surface ($\text{Pt}/\text{Al}^{3+}_{\text{penta}} = 1$), whereas two-dimensional Pt rafts form at higher coverages.

The ability to control the dispersion and morphology (typical characteristics that determine the performance of catalysts) of oxide-supported metal catalysts is a primary goal of catalyst design and can be enabled by understanding the nature of metal-support surface interactions. Precious metals (e.g., Pt, Pd, and Rh) supported on oxide surfaces are the most widely used industrial catalyst materials. For these classes of catalysts, dispersion of the precious metal on the oxide support is an especially critical factor because of the expense of the metal.

The so-called strong metal-support interaction (SMSI) is often seen as critical to sustaining

high catalytic activity under demanding catalyst operation conditions (i.e., high temperature, high water vapor pressure, etc.). Indeed, SMSI has been directly linked to the presence of electronic defects that can be prepared with ease on the surfaces of reducible oxides (e.g., CeO_2 and TiO_2) (1). Anchoring the active metal components to these electronic defects has been documented (2, 3), with the strong interaction between the active metal and defects of reducible oxides fundamentally determining the dispersion, morphology, and, therefore, the catalytic activity of metal clusters. For example, the correlation between the number of oxygen defects on the TiO_2 support and the dispersion and morphology of nanosized Au particles has been clearly demonstrated by the results of density functional theory (DFT) calculations of Lopez *et al.* (2). Experimentally, Chen and Goodman (3) have described the formation of stable, two-dimensional (2D) Au clusters on a defect-rich TiO_2 thin film.

Electronic defects, however, are not present on $\gamma\text{-Al}_2\text{O}_3$, a nonreducible oxide that is one of

the most commonly used catalyst support materials in practical applications. Still, high dispersion and thermal stability of the active metal phase can be achieved and maintained on $\gamma\text{-Al}_2\text{O}_3$ supports, with Koningsberger and co-workers (4) suggesting that specific interactions between “defect sites” of $\gamma\text{-Al}_2\text{O}_3$ and Pt clusters play an essential role. Their extended x-ray absorption fine structure (EXAFS) analysis revealed changes in the morphology of $\gamma\text{-Al}_2\text{O}_3$ -supported Pt particles upon annealing at 723 K. In particular, 3D Pt particles were converted into 2D rafts during the annealing process. Additional evidence for the presence of special (so-called “defect”) sites for anchoring precious metals comes from the presence of monoatomically dispersed Pt on $\gamma\text{-Al}_2\text{O}_3$ in high-angle annular dark-field scanning transmission electron microscopy (HA-ADF STEM) images reported by Pennycuik and co-workers (5, 6). However, in spite of considerable efforts to understand the interaction between catalytically active metal particles and $\gamma\text{-Al}_2\text{O}_3$ support surfaces, the exact nature of the defect sites where these metals can anchor and be stabilized has not been determined (4, 7–9). We present data obtained from ultrahigh magnetic field ^{27}Al magic-angle spinning (MAS) nuclear magnetic resonance (NMR) spectroscopy and HA-ADF STEM techniques that suggest that coordinatively unsaturated Al^{3+} centers [i.e., pentacoordinate Al^{3+} ($\text{Al}^{3+}_{\text{penta}}$)] on the $\gamma\text{-Al}_2\text{O}_3$ surface are the anchoring sites for PtO, the precursor of metallic Pt. We used DFT to confirm the experimental observations for the feasibility of the formation of 2D PtO rafts interacting with $\text{Al}^{3+}_{\text{penta}}$ surface sites on the $\gamma\text{-Al}_2\text{O}_3$ support surface.

High-resolution ^{27}Al solid state MAS-NMR spectra collected at ultrahigh magnetic fields for the $\gamma\text{-Al}_2\text{O}_3$ support and 10 weight percent (wt %) Pt/ $\gamma\text{-Al}_2\text{O}_3$ samples after annealing at 573 K are displayed in Fig. 1A. The spectrum of the metal-free oxide support exhibits three peaks centered at 13, 35, and 70 parts per million (ppm) chemical shifts [referenced to 1 M aqueous $\text{Al}(\text{NO}_3)_3$]. The two characteristic ^{27}Al NMR features of $\gamma\text{-Al}_2\text{O}_3$ at 13 and 70 ppm represent Al^{3+} ions in octa-

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hedral ($\text{Al}^{3+}_{\text{octa}}$) and tetrahedral ($\text{Al}^{3+}_{\text{tetra}}$) coordination, respectively. The NMR peak at 35 ppm chemical shift has been assigned to Al^{3+} ions in pentahedral coordination ($\text{Al}^{3+}_{\text{penta}}$) (10, 11). These pentacoordinate sites are created on the $\gamma\text{-Al}_2\text{O}_3$ surface by dehydration and dehydroxylation at elevated temperatures (here at 573 K) (10, 11). Loading Pt onto the $\gamma\text{-Al}_2\text{O}_3$ support and calcining the catalyst material at 573 K result in a substantial decrease in the number of $\text{Al}^{3+}_{\text{penta}}$ sites, as evidenced by the large drop in the intensity of the 35-ppm NMR peak. Concomitantly, the intensity of the 13-ppm NMR feature increases with the loading of Pt onto $\gamma\text{-Al}_2\text{O}_3$, which suggests the conversion of the $\text{Al}^{3+}_{\text{penta}}$ sites into $\text{Al}^{3+}_{\text{octa}}$ (coordinative saturation; the total number of Al^{3+} ions remains constant). These results strongly suggest that Pt atoms bind to the $\text{Al}^{3+}_{\text{penta}}$ sites on the $\gamma\text{-Al}_2\text{O}_3$ surface through oxygen bridges, thereby coordinatively saturating these sites (penta- to octahedral conversion).

Quantitative evaluation of the number of $\text{Al}^{3+}_{\text{penta}}$ sites (exclusively present on the surface of the oxide support) converted to $\text{Al}^{3+}_{\text{octa}}$ sites by the addition of Pt is made possible by using the NMR peak areas in Fig. 1A and the results of our previous work on $\text{BaO}/\gamma\text{-Al}_2\text{O}_3$ systems (11, 12). The number of $\text{Al}^{3+}_{\text{penta}}$ sites on the metal-free, 573 K-calcined $\gamma\text{-Al}_2\text{O}_3$ sample has been estimated to be 1.8×10^{-4} mole/g (11), whereas the number of Pt-free $\text{Al}^{3+}_{\text{penta}}$ surface sites still present after 10 wt % Pt loading is about 0.7×10^{-4} mole/g. With the known total amount of Pt in the catalyst, the difference between the number of $\text{Al}^{3+}_{\text{penta}}$ sites before and after Pt loading can be used to estimate the average number of Pt atoms per reacted (i.e., converted to $\text{Al}^{3+}_{\text{octa}}$) pentacoordinate surface Al^{3+} ions. Assuming an even distribution of Pt on the $\gamma\text{-Al}_2\text{O}_3$ surface, on average, ~one of every four Pt atoms is anchored to each of the occupied $\text{Al}^{3+}_{\text{penta}}$ sites. HA-ADF STEM images obtained from this sample (dis-

cussed later) show the formation of 2D raftlike Pt structures. Thus, the strong interactions between some Pt atoms in these clusters and the $\text{Al}^{3+}_{\text{penta}}$ sites on the $\gamma\text{-Al}_2\text{O}_3$ surface are likely responsible for the formation of 2D Pt rafts.

All of these results suggest that Pt is selectively anchored to the pentacoordinate aluminum ions present on the surface of mildly calcined $\gamma\text{-Al}_2\text{O}_3$. Thus, we propose that the coordinative saturation of these pentacoordinate aluminum ion sites is the driving force for the strong catalytic active phase-support interaction. This structure represents a fundamentally different anchoring of the active catalyst component onto the oxide support from the SMSI observed in metal-reducible support oxide catalyst systems. For $\gamma\text{-Al}_2\text{O}_3$, the driving force is the coordinative saturation of specific sites on the support oxide surface (i.e., $\text{Al}^{3+}_{\text{penta}}$), whereas in reducible oxides it is an electronic interaction between the metal and the electronic defects on/in the oxide (2). The interaction between Pt and $\gamma\text{-Al}_2\text{O}_3$ surface described here is similar to our recent discussion of specific interactions between oxides (e.g., BaO and La_2O_3) and $\text{Al}^{3+}_{\text{penta}}$ sites on $\gamma\text{-Al}_2\text{O}_3$ (11–13). In this work, such interactions were shown to be responsible for the thermal stabilization of the $\gamma\text{-Al}_2\text{O}_3$ structure. Pentacoordinate Al^{3+} ions formed on the (100) facets of $\gamma\text{-Al}_2\text{O}_3$ upon high-temperature calcination interacted selectively with these oxides, forming highly (even atomically) dispersed nanostructures (12).

The number of $\text{Al}^{3+}_{\text{penta}}$ sites increases with increasing annealing temperature. For example, Fig. 1B shows the number of $\text{Al}^{3+}_{\text{penta}}$ sites (determined from NMR spectra) as a function of calcination temperature for $\gamma\text{-Al}_2\text{O}_3$ and 10 wt % Pt/ $\gamma\text{-Al}_2\text{O}_3$. As the temperature was raised from 573 K to 873 K, the number of $\text{Al}^{3+}_{\text{penta}}$ sites increased from 1.8×10^{-4} to 2.8×10^{-4} mole/g for the metal-free $\gamma\text{-Al}_2\text{O}_3$ support, whereas it changed from 0.7×10^{-4} to 2.1×10^{-4} mole/g

for the 10 wt % Pt/ $\gamma\text{-Al}_2\text{O}_3$ catalyst. The results presented in Fig. 1B reveal that, although the number of $\text{Al}^{3+}_{\text{penta}}$ sites increased on both metal-free and metal-loaded $\gamma\text{-Al}_2\text{O}_3$ support, the difference in the number of $\text{Al}^{3+}_{\text{penta}}$ centers between the clean and metal-loaded support decreased substantially as the calcination temperature increased. As described above, we can estimate the average number of Pt atoms per occupied $\text{Al}^{3+}_{\text{penta}}$ [denoted in the following as $\text{Pt}/\text{Al}^{3+}_{\text{penta}}(\text{occupied by Pt})$] as a function of calcination temperature (red symbols in Fig. 1B) by using the experimental values of occupied $\text{Al}^{3+}_{\text{penta}}$ sites and the known quantity of Pt in the catalyst. At 573 K, the number of $\text{Pt}/\text{Al}^{3+}_{\text{penta}}(\text{occupied by Pt})$ is ~four (as we have discussed previously), and this number is unchanged as the calcination temperature is raised to 673 K. As the sample is calcined to even higher temperatures (773 and 873 K), the number of $\text{Pt}/\text{Al}^{3+}_{\text{penta}}(\text{occupied by Pt})$ approximately doubled. The observed stepwise increase above 673 K calcination temperature can be explained by the sintering of metallic Pt particles that begin to form at around 723 K even under oxidizing conditions.

Given evidence for a specific and strong interaction between Pt and the $\text{Al}^{3+}_{\text{penta}}$ sites, can we control the number of $\text{Pt}/\text{Al}^{3+}_{\text{penta}}(\text{occupied by Pt})$ during catalyst preparation? This parameter ultimately determines the dispersion and likely also the morphology of the active metal phase supported on $\gamma\text{-Al}_2\text{O}_3$. Theoretical studies of the structure of $\gamma\text{-Al}_2\text{O}_3$ have predicted that the (100) crystal facets (representing about 17% of the total surface area) readily dehydrate and dehydroxylate under conditions of calcination applied throughout this study, producing the stable $\text{Al}^{3+}_{\text{penta}}$ sites (14, 15). By keeping the number of $\text{Al}^{3+}_{\text{penta}}$ sites constant (calcining the samples to the same temperature of 573 K) and varying the loading of Pt, we can prepare catalysts with a range of $\text{Pt}/\text{Al}^{3+}_{\text{penta}}(\text{occupied by Pt})$ values. To

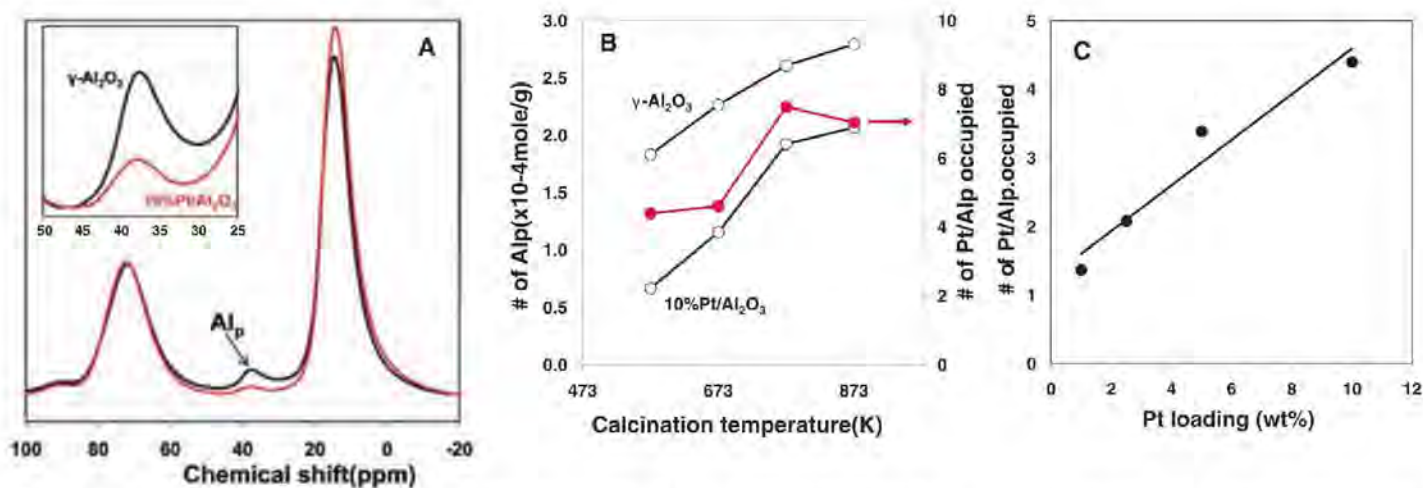


Fig. 1. (A) The ^{27}Al MAS-NMR spectra of $\gamma\text{-Al}_2\text{O}_3$ (black) and 10 wt % Pt/ $\gamma\text{-Al}_2\text{O}_3$ (red) (both samples were calcined at 573 K before NMR measurements). (B) Number of $\text{Al}^{3+}_{\text{penta}}$ sites as a function of calcination temperature in $\gamma\text{-Al}_2\text{O}_3$ (black) and 10 wt % Pt/ $\gamma\text{-Al}_2\text{O}_3$ (blue) samples. The

number of Pt per $\text{Al}^{3+}_{\text{penta}}$ site as a function of calcination temperature is displayed in red. (C) The number of Pt atoms per $\text{Al}^{3+}_{\text{penta}}$ sites as a function of Pt loading on $\gamma\text{-Al}_2\text{O}_3$ support. (Samples were calcined at 573 K before NMR measurements.)

this end, we prepared a series of Pt/ γ -Al₂O₃ catalysts with a range of Pt loading of 1 to 10 wt %. After calcining the samples under identical conditions (573 K), the number of Al³⁺_{penta} ions was estimated for each Pt-loaded sample by ultrahigh magnetic field ²⁷Al MAS-NMR. These measurements again allowed us to quantitatively determine the average number of Pt/Al³⁺_{penta} (occupied by Pt), and the results are displayed in Fig. 1C. Interestingly, a practically linear relation was found between the Pt/Al³⁺_{penta} (occupied by Pt) and the Pt loading in the coverage range of this study.

The results presented in Fig. 1C suggest that, at loadings of 1 wt % Pt or lower, each occupied Al³⁺_{penta} site interacts with exactly one Pt atom, meaning that all Pt must be atomically dispersed. This result [Pt/Al³⁺_{penta} (occupied by Pt) = 1] is similar to our observations for a 2 wt % BaO/ γ -Al₂O₃ sample calcined at 773 K (12). In the latter case, HA-ADF STEM images revealed the presence of mostly single BaO units dispersed on certain, most likely (100), facets of the γ -Al₂O₃ support. In order to substantiate our claim of single-atom Pt

dispersion at loadings ≤ 1 wt %, we collected HA-ADF STEM images for the 1 wt % Pt/ γ -Al₂O₃ sample calcined at 573 K. The HA-ADF STEM image shown in Fig. 2A demonstrates the almost-perfect atomic dispersion of Pt on the γ -Al₂O₃ surface at 1 wt % loading. Atomic dispersion of Pt on γ -Al₂O₃ at low loadings has been observed previously in a STEM study (5, 6); however, the nature of the sites where Pt was anchored to the support surface had not been elucidated.

At higher Pt loadings, the formation of 2D Pt rafts has been proposed on the basis of the results of Pt EXAFS measurements (4). The NMR results presented here also suggest the formation of PtO clusters on the Al³⁺_{penta} sites, consisting on average of four Pt atoms per anchoring site at 10 wt % loading after calcination at 573 K. HA-ADF STEM images, obtained after calcination of a 10 wt % Pt-loaded sample at 573 K (Fig. 2, B to D), substantiate the formation of 2D Pt rafts on the γ -Al₂O₃ surface with 1-nm average size. The high-resolution image in Fig. 2C also reveals that a substantial fraction of atomically dispersed

Pt is still present on the γ -Al₂O₃ surface, presumably bound to Al³⁺_{penta} surface sites as evidenced by the NMR and HA-ADF STEM results obtained at lower Pt loadings. The 2D rafts (a good representative close-up image is shown in Fig. 2D) with 1-nm average size consist of about 20 Pt atoms, suggesting that these rafts may interact with as many as four to five Al³⁺_{penta} sites in order to maintain the average of ~ 4 Pt/Al³⁺_{penta} (occupied by Pt) ratio. From cross sections of one of the images (Fig. 2, E and F), the distance between two Pt atoms is estimated to be 2.78 Å, shorter than the expected Pt-Pt distances in PtO (3.1 Å) and almost identical to the bond distance in metallic Pt (2.76 Å). However, the results of x-ray absorption near-edge structure analysis substantiate that the rafts observed after 573 K calcination are PtO (fig. S1) (16).

Analysis of a number of cross sections on different particles also supports the assignment of these PtO particles to 2D rafts instead of 3D clusters. Furthermore, DFT calculations (discussed below) suggest a Pt-Pt distance of 2.8 Å in 2D PtO overlayers on γ -Al₂O₃(100) facets. On the basis of DFT calculations, Lopez *et al.* (2) recently proposed the formation of 2D metallic gold rafts over defect sites of a TiO₂(110) surface. The formation of 2D Au rafts on the defect sites of a TiO₂ film was experimentally confirmed by Chen and Goodman (3). The strong interaction between Au and electronic defects (oxygen vacancies) on TiO₂ results in the formation of 2D metallic particles. In our system, the strong interaction between PtO and the coordinatively unsaturated Al³⁺_{penta} sites on the γ -Al₂O₃ surface is responsible for the formation of PtO rafts (4, 17).

In order to further substantiate the role of Al³⁺_{penta} sites in determining Pt dispersion and, thus, morphology on alumina supports, we compared the above results obtained on γ -Al₂O₃ with high-resolution STEM (HR-STEM) images for a 0.25 wt % Pt/ α -Al₂O₃ catalyst calcined at 573 K. The low Pt loading on the low-surface-area α -Al₂O₃ support was chosen to match the Pt/support sur-

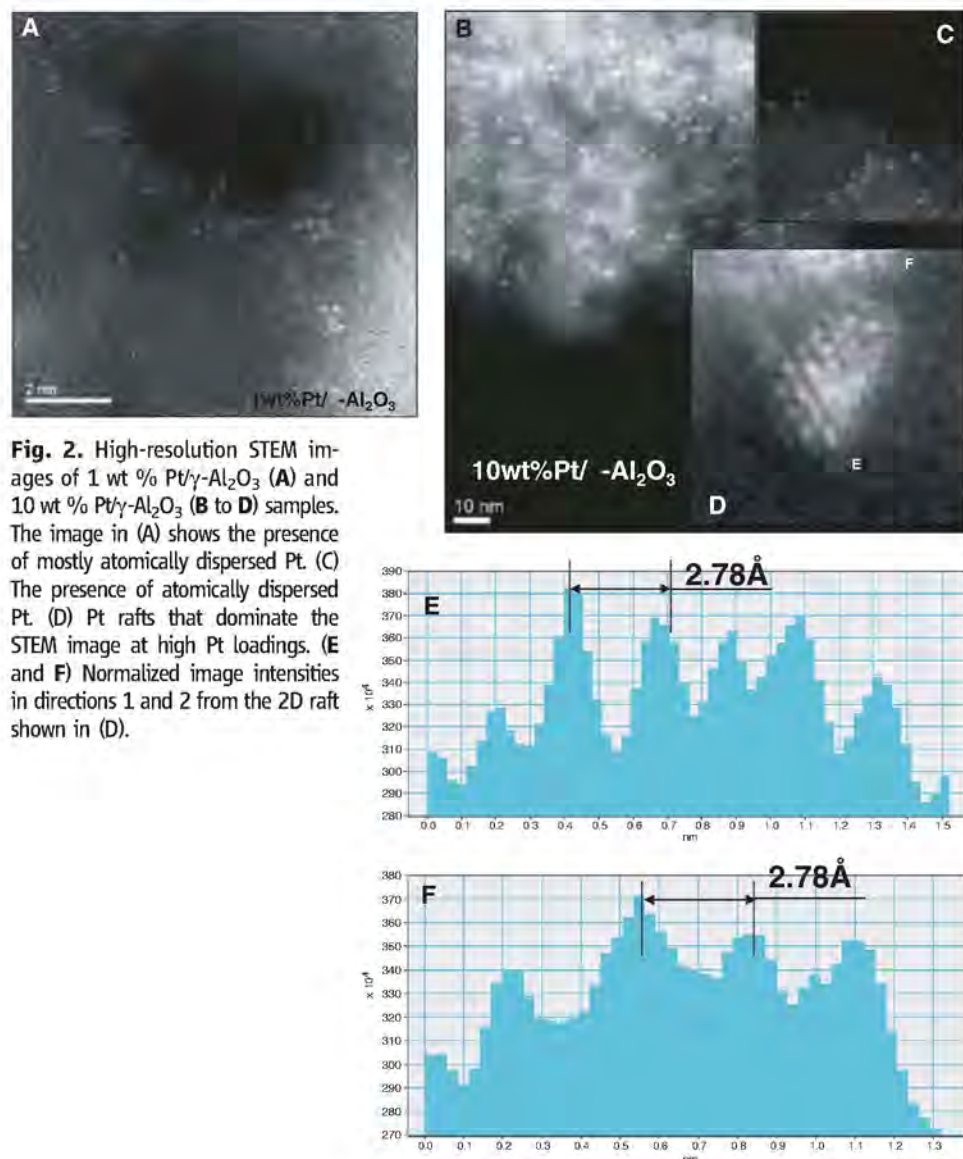


Fig. 2. High-resolution STEM images of 1 wt % Pt/ γ -Al₂O₃ (A) and 10 wt % Pt/ γ -Al₂O₃ (B to D) samples. The image in (A) shows the presence of mostly atomically dispersed Pt. (C) The presence of atomically dispersed Pt. (D) Pt rafts that dominate the STEM image at high Pt loadings. (E and F) Normalized image intensities in directions 1 and 2 from the 2D raft shown in (D).

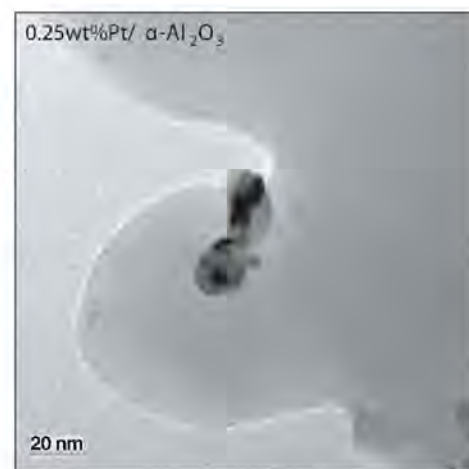


Fig. 3. TEM image of a 0.25 wt % Pt/ α -Al₂O₃ sample obtained after calcination at 573 K.

face area ratio of the 10 wt % Pt/ γ - Al_2O_3 sample. A representative TEM image (Fig. 3) shows the formation of very large 3D Pt particles (10 to 15 nm) on the α - Al_2O_3 support, even after the relatively low-temperature (573 K) calcination. The formation of these large Pt clusters on the α - Al_2O_3 support indicates a very weak interaction between PtO and the support. The particles can readily migrate even at this relatively low calcination temperature because the α - Al_2O_3 surface does not possess any $\text{Al}^{3+}_{\text{penta}}$ sites (18) that would provide anchoring points for PtO to the surface. Another consequence of the weak interaction between PtO and α - Al_2O_3 is the formation of metallic Pt upon calcination at temperatures as low as 573 K. Reduction temperatures increase with increasing catalyst precursor (here PtO)-support oxide interaction in supported Pt catalysts (17).

We performed DFT calculations (16) in order to obtain specific information about (i) the energetics of the interaction of PtO particles with the (100) facets of γ - Al_2O_3 and (ii) the likely stable structures of the experimentally (HA-ADF STEM) observed 2D PtO rafts. The surface model for γ - Al_2O_3 was taken from the work of Digne *et al.* (14, 15) that showed the formation of pentacoordinated Al^{3+} ions on the (100) facets upon termination of the bulk structure. The γ - Al_2O_3 (100)- 2×1 surface model used in this work consists of eight Al_2O_3 units with all surface Al^{3+} ions being pentacoordinated and the O^{2-} ions tricoordinated. Our calculations, in agreement with those reported previously (14, 15), indicate that the γ - Al_2O_3 (100) surface was fully dehydrated under the experimental conditions of this study (i.e., 573-K calcination). Various structures extracted from one layer of an optimized tetragonal PtO bulk on the γ - Al_2O_3 (100) surface were examined. The O-terminated PtO(101) struc-

ture on the γ - Al_2O_3 (100) surface was the thermodynamically most stable structure. Interestingly, this PtO(101) overlayer structure was obtained from the relaxation of an O-terminated PtO(100) structure on the γ - Al_2O_3 (100) surface. The relaxation can be attributed to the thermodynamic instability of the PtO(100) surface, which has a negative surface energy (19). The 2D PtO(101) overlayer (Fig. 4) strongly interacts with the γ - Al_2O_3 (100) surface via four O- $\text{Al}^{3+}_{\text{penta}}$ bonds, with a binding energy of 7.1 eV. The ratio of PtO/ $\text{Al}^{3+}_{\text{penta}}$ (occupied by Pt) is three, similar to our experimental estimation of about four (although it should be noted that the experimental number is affected by the presence of atomically dispersed Pt evident in the HA-ADF STEM images). The Pt-Pt bond lengths in the 2D PtO overlayer structure after relaxation are calculated to be between 2.7 and 2.9 Å, in excellent agreement with the 2.78 Å estimated from the HR-STEM images.

The work presented here provides a new understanding about the nature of strong interactions between catalytic phases and oxide support materials in the industrially important catalyst system, Pt/ γ - Al_2O_3 . Our explanation for the role of pentacoordinated Al^{3+} ions in the anchoring of the catalytically active phase (Pt) to the γ - Al_2O_3 support is arrived at on the basis of the results of ultrahigh magnetic field ^{27}Al MAS-NMR measurements. At low (≤ 1 wt %) Pt loadings, Pt is atomically dispersed on the support surface (Pt/ $\text{Al}^{3+}_{\text{penta}} = 1$). When the loading of Pt exceeds the number of $\text{Al}^{3+}_{\text{penta}}$ sites, 2D PtO rafts form, as evidenced by HA-ADF STEM measurements. DFT calculations provide further confirmation for the energetic feasibility of the formation of these 2D rafts as well as for their energetically most stable overlayer structure. (Although data

presented here are consistent with the mechanism of Pt anchoring to the $\text{Al}^{3+}_{\text{penta}}$ sites of γ - Al_2O_3 , other mechanisms, including the reaction between the $\text{Al}^{3+}_{\text{penta}}$ sites and the ligands of the Pt precursor, cannot be completely ruled out.) A substantial challenge remains to develop synthesis methods that allow for the systematic and controllable variation of the number of $\text{Al}^{3+}_{\text{penta}}$ sites, ultimately enabling us to tailor the dispersion and morphology and, therefore, catalytic activity of active metals on the commonly used γ - Al_2O_3 support material.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5948/1670/DC1
Materials and Methods

SOM Text

Fig. S1

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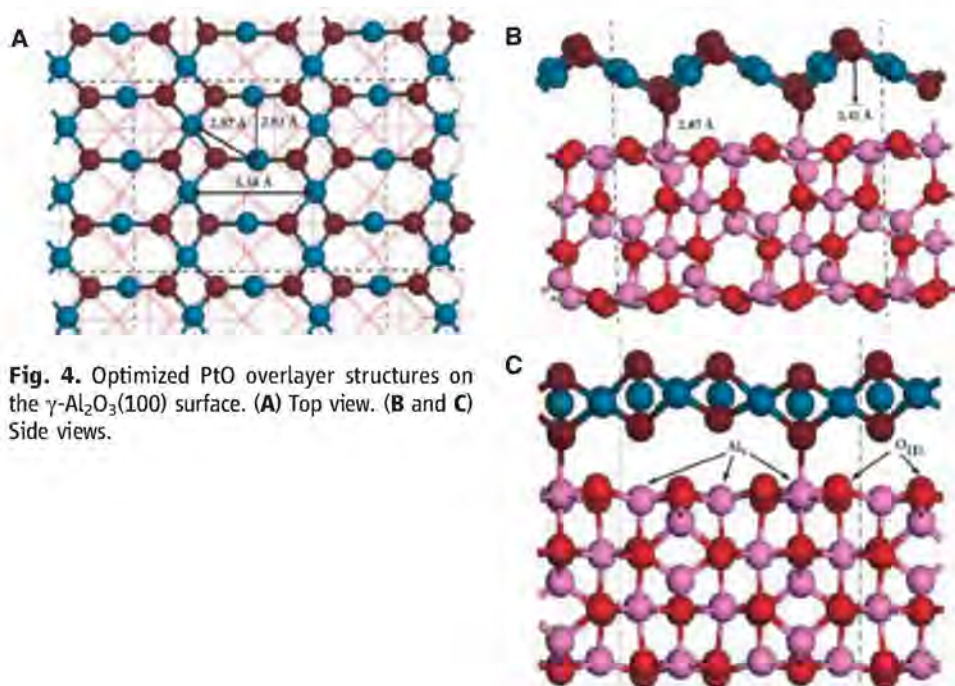


Fig. 4. Optimized PtO overlayer structures on the γ - Al_2O_3 (100) surface. (A) Top view. (B and C) Side views.

Distribution of Mid-Latitude Ground Ice on Mars from New Impact Craters

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New impact craters at five sites in the martian mid-latitudes excavated material from depths of decimeters that has a brightness and color indicative of water ice. Near-infrared spectra of the largest example confirm this composition, and repeated imaging showed fading over several months, as expected for sublimating ice. Thermal models of one site show that millimeters of sublimation occurred during this fading period, indicating clean ice rather than ice in soil pores. Our derived ice-table depths are consistent with models using higher long-term average atmospheric water vapor content than present values. Craters at most of these sites may have excavated completely through this clean ice, probing the ice table to previously unsampled depths of meters and revealing substantial heterogeneity in the vertical distribution of the ice itself.

Using theoretical models, previous investigators predicted that buried water ice is stable at high latitudes on Mars beneath a desiccated soil layer (1–4) with an extent and depth that depend on temperature and humidity (which vary with changing orbital elements). Hydrogen abundances inferred from gamma-ray, high-energy neutron and neutron spectrometer (NS) data show that the uppermost decimeters of the martian surface contain large amounts of water ice poleward of latitudes $\pm 60^\circ$ (5–8), which can exceed 50% by mass (~75% by volume). A key parameter setting the extent of stable ground ice is the global average atmospheric water vapor. Models suggest 20 precipitable micrometers (pr- μm) best explains the NS data (9), whereas direct measurements indicate only 14 pr- μm (10) or perhaps even lower (11). The mid-latitude boundary enclosing the area where buried ice is presently stable is expected to be abrupt (Fig. 1), and its position is sensitive to this long-term global average (higher atmospheric water vapor results in increased ice stability). However, the NS data (Fig. 1) cannot tightly constrain the location of this abrupt edge (12), and although the NS can constrain the depth to the top of the high-latitude ice table, it is insensitive to changes in ice concentration a few centimeters below that (13).

Here, we report on a method to probe subsurface ice on Mars. Impact craters with meter-to decameter-scale diameters form frequently (14). Analysis of Context Camera (15) (CTX) images led to the identification of five such

impacts (Fig. 1) near the boundary of Utopia and Arcadia Planitia [see the supporting online material (SOM) for details]. Follow-up observations by the High-Resolution Imaging Science Experiment (HiRISE) (16) showed the excavated material to have brightness and color indicative of water ice (Figs. 2 and 3). Impact times are constrained by images taken before and after impact (Table 1).

We examined hyperspectral data from the Compact Reconnaissance Imaging Spectrometer for Mars (CRISM) (17) covering these sites for spectral signatures of water ice. In general, the bright material imaged by HiRISE occupies only a few percent of a CRISM pixel (18 m across); however, bright material at site 3 was extensive enough to occupy a substantial fraction of several CRISM pixels. Water ice absorption bands were detected over this feature, but not over adjacent terrain (Fig. 3). The other sites do not show spectral evidence of ice, likely due to their small areas (next largest is site 5, occupying ~0.1 CRISM pixels).

Site 1 contains a cluster of small craters of which many have flat floors, indicating excavation to a mechanically stronger material. Icy material appears in two such craters. Site 5 contains a single crater with isolated interior decimeter-scale spots of ice and a larger (4 m by 9 m) exterior icy

patch adjacent to the crater's eastern side only (although the crater and its 1-km-long dark rays are symmetric). Aeolian action may have transported ice within the crater over its eastern rim, a direction consistent with nearby wind observations (18). Sites 1 and 5 contain well-developed polygons (7 to 8 m across). Sites 2 and 4 occur in the Phlegra Montes, eroded massifs with associated debris-covered aprons. Site 2 (and perhaps sites 1 and 4) occurs on these lobate aprons, once interpreted as ice-rich debris (19); however, similar aprons elsewhere are now known to be composed of relatively pure ice (20, 21). Sites 2 and 4 have ice on their interior crater walls and draped over their rims. Site 3, on dark plains, has excavated subsurface ice almost entirely onto its ejecta blanket. We interpret the absence of bright ice on the crater floor at sites 2 to 5 to indicate that these impacts excavated completely through a relatively thin buried bright ice layer. Other, less likely, alternatives include obscuration by dust fallout (which would not concentrate at the crater bottom), saltating particles collecting inside the crater (no dunes or ripples indicates the presence of such particles in this region), fallback of crater ejecta (yet site 3 ejecta is ice-rich and the crater floor is dark), and slumping of regolith from the walls [however, the site 3 regolith layer is thought to be only 12 cm thick (9), and no slumping occurred at site 1]. Bright ice on site 1 crater floors indicates excavation to the bright icy layer, but not through it, consistent with derived crater depths (Table 1).

Monitoring by HiRISE (Fig. 2 and fig. S2) has shown changes in the excavated bright material at all sites, consistent with sublimation of water ice. Exposed mid-latitude water ice is expected to sublimate, causing darkening and reddening as debris within the ice accumulates as a soil lag. Figure 2 shows a clear fading and reddening of icy material at site 1 (its bright blue appearance disappeared over 140 to 200 days). To quantify the total sublimation in this interval, we constructed a one-dimensional thermal model (see SOM). We simulated a dry soil layer with underlying ice to establish the pre-impact subsurface temperatures. We then removed the soil layer and followed the ice surface temperature to calculate sublimation. Among many parameters, the most influential were wind speed

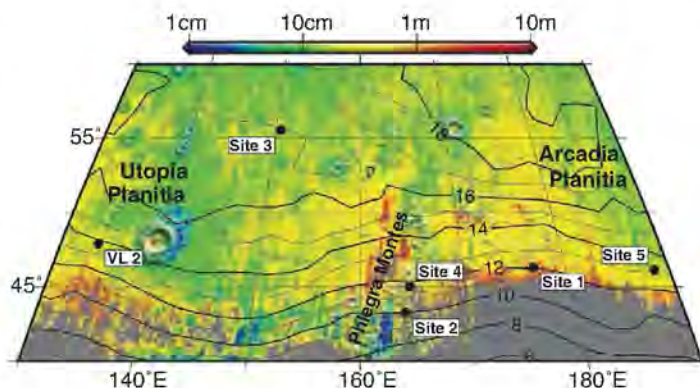


Fig. 1. Expected ice depths (9) with Viking Lander 2 and sites 1 to 5 labeled. Contours represent ice depths (g/cm^2) derived from NS data. Replotted from data in (8).

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Fig. 2. HiRISE false-color data (see Table 1 for image details) showing sublimation of icy material at site 1. Panels are 75 m across. Images here and in Fig. 3 have north at the top and are illuminated from the lower left. Plot shows the brightness evolution of the lower-right icy patch (solid) and dark impact zone (dashed) in each HiRISE filter scaled by the brightness of the surrounding undisturbed terrain (to remove incidence angle and first-order atmospheric effects). Vertical lines show observation dates. Blue-green and near-infrared bands at L_s 126° were summed 4×4 .

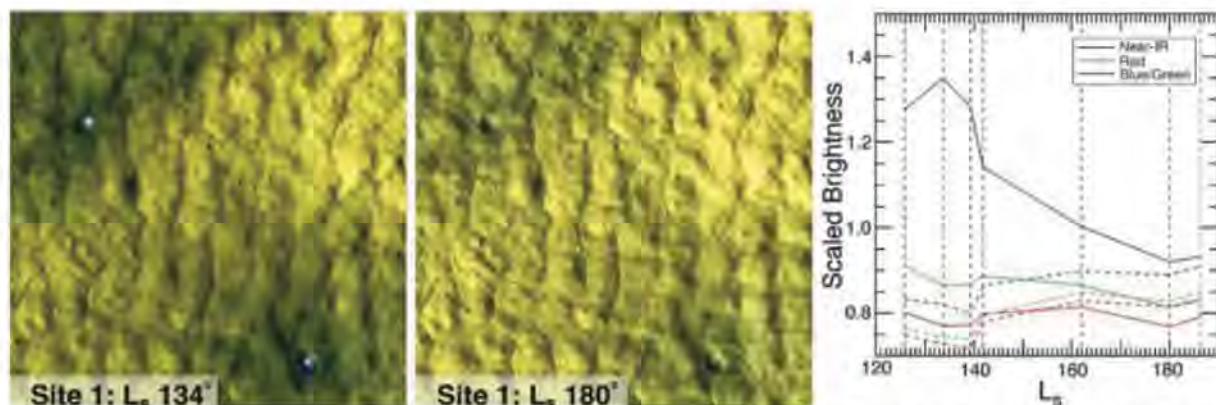
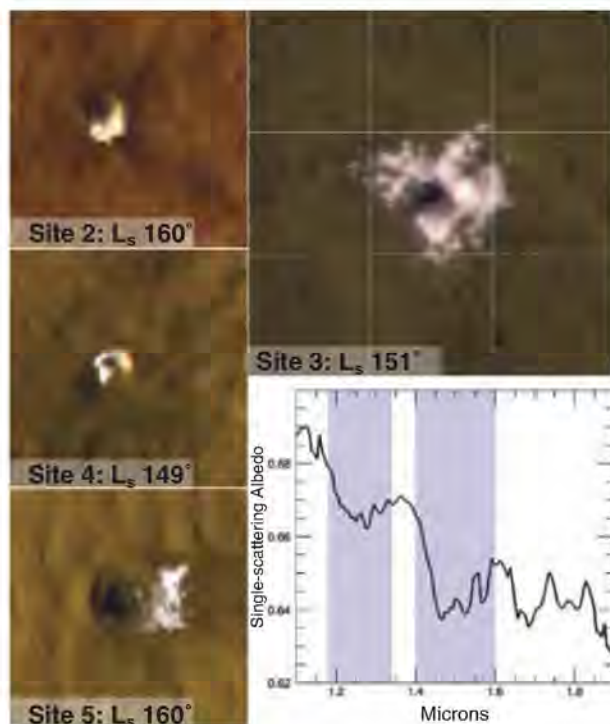


Fig. 3. HiRISE false-color data of sites 2 to 5 (see Table 1 for image details). Left panels are 35 m across; gridlines at site 3 show the scale (18 m) (but not location) of CRISM pixels. CRISM spectrum at lower right with water ice absorption bands indicated is an average of four adjacent pixels in observation FRT0000D2F7.



(nominally 2.5 m s^{-1}) and initial ice albedo (nominally 0.4), which we darkened linearly to background levels by L_s 171°. Varying all parameters within reasonable ranges yielded total sublimations of 0.3 to 6.5 mm, with our nominal case yielding 1.7 mm. Purposefully conservative choices in environmental and physical parameters make this sublimated thickness a robust lower limit (see SOM).

Our estimate of sublimation at site 1 while this ice is fading to background brightness implies clean ice. Experiments indicate that as little as $17 \mu\text{m}$ of dust masks bright white material at wavelengths of HiRISE's blue-green filter (16, 22). Fading caused by a sublimation lag of dust-sized particles thus implies a debris concentration of only 1% (an upper limit because the sublimation estimate is conservative). The surrounding dark areas (regions blown clear of dust) brighten toward the level of adjacent undisturbed terrain,

indicating that atmospheric dust is settling out on the surface. This implies that some of the fading of the ice is caused by this dust fallout rather than by a sublimation lag. Hence, the ice's dust content may be even lower than discussed above. Similarly, if some darkening were caused by ice-grain growth via thermal metamorphism (23), then the ice would be even cleaner than derived. Aeolian removal of dust could counter darkening, causing an underestimate of dust content. This is unlikely because brightening of the dark areas indicates dust accumulation. Ice exposed at site 1 is not pore-filling ice, but is relatively pure, at least in the uppermost millimeters. Sites 2, 4, and 5 are at similar latitude and fade at similar rates (fig. S2), implying that this ice is similarly pure. Site 3 (at higher latitude) is fading and shrinking at a slower rate, as expected. It is unlikely that these small impacts can clean ground ice by melting, because melt should easi-

ly drain through the ejecta blanket or heavily fractured crater floor.

These craters formed near the abrupt transition from where ground ice is expected to be stable to where it is not (Fig. 1). Here, the expected depth to ice in models is very sensitive to latitude (fig. S4), and its presence in these shallow craters provides a strong test of these models. Results of models using 20 μm of atmospheric water vapor (9) agree very well (Table 1) with our data (whereas ground ice at these sites is not expected with 10 μm). Two craters at site 1 appear to have exposed the top of the ice table, and their depths coincide closely with the expected ice-table depth. Sites 2 to 5 have crater depths exceeding the model-predicted depth to ground ice; excavation of ice here is consistent with model results (depth could not be measured for site 3; however, 8-m craters excavate $>12 \text{ cm}$). The Phoenix lander encountered both ice-cemented soil and clean ice at 68°N , 234°E (24) at depths close to model predictions (25). Viking Lander 2 (Fig. 1) dug trenches $\sim 15 \text{ cm}$ deep at 48°N (26) and did not discover ice (the model predicts ice at 24 cm). Given our observations, it is likely that ice exists here slightly deeper than excavated to in the 1970s.

The highest-latitude ice-free craters could place an upper limit on the long-term average of atmospheric water vapor. Six new craters poleward of 30°N (and at lower latitudes than sites 1 to 5) that do not show evidence of this bright ice are known (table S1). However, ice at site 1 became unrecognizable within months, and all these craters may be up to years old, so their current ice-free appearance may not indicate a lack of the clean ice layer at these locations (further discussion in the SOM).

The origin of this clean ice is not obvious. It can be removed by diffusion to the atmosphere, but diffusion of vapor into the regolith creates only pore-filling ice. Burial of dusty snow (27) deposited during high obliquities (perhaps as recently as $\sim 400,000$ years ago when obliquity was 30°) has been suggested, yet simulations (4, 28, 29) indicate that buried ice at this latitude is efficiently removed during low-obliquity pe-

Table 1. Timing, locations and observations of sites 1 to 5. Martian dates are given by aerocentric longitude of the Sun (L_s) and Mars year (M29 started 12/2007). Image names beginning with V are from the Thermal Emission Imaging System visible camera; names beginning with P/B are from CTX and abbreviated (full names: P22_009556_2263_XI_46N183W, P20_008699_2247_XN_44N182W, P21_009095_2225_XN_42N195W,

B01_010058_2375_XN_57N209W, B01_010018_2247_XN_44N195W, and P20_009015_2262_XI_46N171W). Crater diameters and depths (shadow measurements) are measured off the HiRISE image (denoted by an asterisk). Both ice-containing craters at site 1 were measured. There was no identifiable shadow at site 3. Rightmost column shows mean and range of predicted ice depths within a 9 km by 9 km region centered on each site (9).

Site	Lon. (°E)	Lat. (°N)	Latest image before impact	Earliest image after impact	HiRISE	L_s M29	Diam. (m)	Depth (m)	Model ice depth (m)
1	176.90°	46.33°	6/4/2008 L_s 81/M29 P20_008699_2247	8/10/2008 L_s 111/M29 P22_009556_2263	PSP_009978_2265	125.9	4	0.55	0.51 (0.36–0.73)
					PSP_010189_2265	133.8			
					PSP_010334_2265	139.3			
					PSP_010400_2265	141.9			
					PSP_010901_2265	162.0			
					ESP_011323_2265*	180.0			
					ESP_011468_2265	186.5			
2	164.22°	43.28°	12/22/2006 L_s 154/M28 V22273012	7/5/2008 L_s 94/M29 P21_009095_2225	PSP_010084_2235	129.8	6	1.33	0.74 (0.34–∞)
					PSP_010440_2235	143.5			
					PSP_010651_2235	151.8			
					ESP_011574_2235*	191.2			
					ESP_011719_2235	197.9			
					ESP_012497_2235	235.1			
3	150.62°	55.57°	1/26/2008 L_s 23/M29 V27128013	9/18/2008 L_s 129/M29 B01_010058_2375	PSP_010625_2360*	150.8	8	?	0.12 (0.09–0.15)
					ESP_011337_2360	180.7			
					ESP_011548_2360	190.1			
4	164.71°	45.05°	1/22/2008 L_s 21/M29 V27090026	9/15/2008 L_s 127/M29 B01_010018_2247	PSP_010585_2255	149.2	6	1.76	0.38 (0.10–∞)
					ESP_011442_2255*	185.3			
					ESP_012220_2255	221.6			
5	188.51°	46.16°	7/3/2004 L_s 55/M27 V11315010	6/28/2008 L_s 92/M29 P20_009015_2262	PSP_010861_2265	160.4	12	2.46	0.14 (0.12–0.16)
					ESP_011283_2265	178.3			
					ESP_011494_2265*	187.6			
					ESP_011850_2265	204.0			

riods (obliquity was 20° ~350,000 years ago). Pure terrestrial ground ice forms quickly by thermomolecular forces (30) from thin films of liquid water (frost heave), and this process may extend to Mars for brines (31). Alternatively, thermal contraction of pore-ice and subsequent vapor deposition may build increasingly pure ground ice, but requires long times (32).

Small, frequent impacts combined with medium- and high-resolution imaging offer a method to gauge the depth and extent of buried ice and probe beneath the top of the ice table. The ice appears to be heterogeneously distributed with depth and includes a relatively clean layer <1 m thick where sampled. Comparing these data with model results tells us about the time-averaged atmospheric water content. The available sites support a value of 20 μm (higher than today's value), indicating current ice-table retreat likely forced by recent orbital change (4, 28, 29).

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Supporting Online Material

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SOM Text

Figs. S1 to S4

Table S1

References

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Holocene Glacier Fluctuations in the Peruvian Andes Indicate Northern Climate Linkages

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The role of the tropics in triggering, transmitting, and amplifying interhemispheric climate signals remains a key debate in paleoclimatology. Tropical glacier fluctuations provide important insight on regional paleoclimatic trends and forcings, but robust chronologies are scarce. Here, we report precise moraine ages from the Cordillera Vilcabamba (13°20'S) of southern Peru that indicate prominent glacial events and associated climatic shifts in the outer tropics during the early Holocene and late in the "Little Ice Age" period. Our glacier chronologies differ from the New Zealand record but are broadly correlative with well-dated glacial records in Europe, suggesting climate linkages between the tropics and the North Atlantic region.

Peru harbors the world's greatest concentration (71%) of present-day tropical glaciers (1) and contains extensive geomorphic features that demarcate former glacier expansion (2). Accurate chronologies of Peru's recent glacial history are key indicators of tropical paleoclimates and are thus critical for evaluating mechanisms of global climate variability and interhemispheric linkages (3). The high sensitivity of tropical mountain glaciers to relatively small-amplitude climate changes makes them particularly useful as indicators of past climatic fluctuations. In addition, understanding past Andean glacier events is imperative for predicting responses to future climate change and consequences for local water resources (4) and vital for identifying environmental impacts on the succession of ancient civilizations in the region (5).

Published chronologies of late Quaternary glacier fluctuations in the central Andes are based on a combination of radiocarbon, lichenometric, and terrestrial cosmogenic nuclide dating methods (6, 7). However, robust age control of Holocene glacial deposits remains notably sparse. Here, we report high-precision cosmogenic ¹⁰Be surface exposure ages of the two most prominent Holocene glacial episodes in the Cordillera Vilcabamba of southern Peru. This new glacial chronology augments nearby ice core (8), lacustrine (9, 10), and marine (11) paleoclimate records.

The field site is located in the vicinity of Nevado Salcantay (6271 m above sea level; 13°20'S, 72°33'W), the highest peak in the Cordillera Vilcabamba (Fig. 1). Glacial troughs

emanating from Salcantay and nearby peaks contain exceptionally well-preserved moraines with large granitic surface boulders. Geomorphic mapping was conducted in the upper Rio Blanco valley south of Salcantay, the Sisaypampa valley east of Salcantay, and the Tucurhuay valley south of adjacent Nevado Tucurhuay (5910 m above sea level). The most prominent moraine sequences in these three drainages are grouped into sharp-crested and largely unweathered "inner" moraines with subangular boulders that commonly preserve glacial polish and "outer" moraines that are more subdued and surfaced with subrounded boulders. Some geomorphic evidence exists for more extensive earlier glacial

episodes, perhaps corresponding to the considerably larger late glacial positions described elsewhere in the tropical Andes (6), but the focus of this study is on the Holocene advances (12).

Samples were collected from 25 boulders atop the outer ($n = 13$) and inner ($n = 12$) moraine crests for ¹⁰Be surface exposure dating (12); data are given in table S1 and age results are plotted in fig. S4. We interpret the arithmetic means of boulder exposure ages from each moraine to reflect the end of moraine construction and, thus, constrain the timing of glacial culminations. The identified patterns of Holocene glaciation and the major conclusions drawn from them are not affected by current uncertainties in ¹⁰Be production rates scaled to our field site (12).

Five of six boulder exposure ages on the Rio Blanco outer moraine show high internal consistency and yield a mean of 8.6 ± 0.3 thousand years ago (ka) ($n = 5$), corresponding to a glacial culmination during the early Holocene (tables S1 and S2). One boulder here (PE06-1; 7.0 ± 0.2 ka) yielded a young outlying age interpreted to indicate a postglacial rockfall. Mean ages on the most distal (9.9 ± 0.7 ka; $n = 4$) and most proximal (8.0 ± 0.5 ka; $n = 2$) ridges of the Sisaypampa outer moraine succession (figs. S2 and S4) flank the age of the Rio Blanco outer moraine and bracket oscillations of a prolonged early Holocene glacial episode. The sole age (4.4 ± 0.1 ka) on the Tucurhuay outer moraine is discordant with ages in the Rio Blanco and Sisaypampa valleys and suspected to reflect postdepositional boulder rotation.



Fig. 1. Geomorphic map of field site. Solid lines show inner (red) and outer (blue) moraines, and arrows show associated outwash; dashed lines indicate inferred locations. White areas represent approximate locations of present-day glaciers in mapped drainages. Base maps from Google Maps.

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Five of seven boulder exposure ages on the Rio Blanco inner moraine yield a tightly clustered mean of 200 ± 20 years [Common Era (CE) 1810 ± 20 ; $n = 5$]. These results are among the youngest ^{10}Be ages reported so far and show that cosmogenic chronologies can be established to overlap historical records and, in turn, modern observations. The high internal consistency of these five ages suggests that isotope inheritance in these very young samples is negligible. However, two ages (PE06-8, 12) from this moraine are old outliers, most likely due to isotope inheritance from previous exposure. Three boulders from the Sisaypampa inner moraine yield a mean age of 240 ± 80 years (C.E. 1770 ± 80 ; $n = 3$). Two boulders atop the largest Tucurhuay inner moraine (fig. S3) yield a mean age of 270 ± 30 years (C.E. 1740 ± 30 ; $n = 2$). Mean ages of inner moraines in all three valleys overlap within 2σ uncertainties and correlate with the late Little Ice Age (LIA), as defined in the Northern Hemisphere and generally considered to extend from ~C.E. 1300 to 1860 (13).

Due to selective preservation of moraine ridges, our records do not exclude the possibility of multiple Holocene glacier expansions. However, the combined geomorphic and geochronologic evidence clearly indicates the dominance of two major episodes in the Cordillera Vilcabamba, including an early Holocene glacial interval and a somewhat less extensive glaciation during the LIA. The early Holocene deposits correlate with moraines ^{10}Be -dated to 8.5 ± 0.7 ka ($n = 7$) in the southern Andes (14), hinting at inter-regional coherency, but documentation for other contemporaneous glacial events in the Andes is sparse (15). Worldwide, well-dated records of early Holocene glacial advances have been developed in only a few locations. End moraines marking the Erdalen Event, an expansion of Jostedalbreen outlet glaciers in southern

Norway, are dated with radiocarbon (16) and ^{10}Be ($n = 3$) (17) to ~ 10.2 to 9.7 ka. The nearby Flatebreen glacier experienced a termination at ~ 10.2 ka and a subsequent expansion from ~ 8.4 to 8.1 ka (18). Moraines in the Austrian Alps were recently dated with ^{10}Be to 10.8 ± 1.0 ka ($n = 3$) and 8.4 ± 0.7 ka ($n = 5$) (19). The ~ 9.9 to ~ 8.0 ka glacial culminations in the Cordillera Vilcabamba are broadly consistent with these European glacier chronologies and similarly correspond to the greatest Holocene extents only ~ 1 to 2 km downvalley from those reached during the LIA.

Moraines related to the LIA in Peru were first radiocarbon-dated more than three decades ago (20), but the limiting ^{14}C age control on recent glacial histories remains of low temporal resolution (6). Lichenometric dating [e.g., (21)] shows the maximum LIA glacier extent around C.E. 1630 ± 30 in the Cordillera Blanca of Peru (7) and from C.E. 1660 ± 20 to C.E. 1690 ± 30 in the eastern Cordilleras of Bolivia (22). These lichen studies also identified successions of moraines ranging from C.E. 1330 ± 30 in the Cordillera Blanca to C.E. 1910 in Bolivia. Notably,

the most recent glacier expansions in the Cordillera Vilcabamba are marked by a single massive moraine ridge, unlike the multiple widely spaced crests in the Cordillera Blanca and in Bolivia. This difference implies contrasting dynamic responses of latest Holocene glaciers in various tropical Andean ranges, perhaps related to differences in glacier size, geometry, and aspect. Moreover, the most precisely dated LIA maximum in the Vilcabamba (C.E. 1810 ± 20) postdates LIA maxima in the Cordillera Blanca and in Bolivia by ~ 180 years and ~ 120 years, respectively, which may be explained in part by uncertainties in lichenometric and ^{10}Be exposure dating methods, but probably indicates real differences in the timing of glacial culminations.

Despite geologic evidence suggesting that the LIA was a global phenomenon (13), exact temporal relationships between worldwide glacier chronologies from this interval are poorly defined due to difficulties in establishing precise moraine ages. Glacial and climatic conditions of the LIA are most thoroughly documented in northern and western Europe by extensive historical accounts,

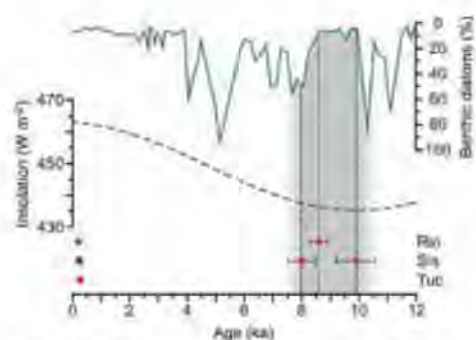


Fig. 2. Timing of Holocene events in southern Peru. Green line shows percentage of benthic diatoms in Lake Titicaca core 1PC (9), with lower percentage of diatoms corresponding to higher lake levels. Dashed blue line shows precessional wet-season (September to March) insolation at 13°S (30). Red diamonds and error bars are means and uncertainties of moraine ages in Rio Blanco (Rio), Sisaypampa (Sis), and Tucurhuay (Tuc) valleys.

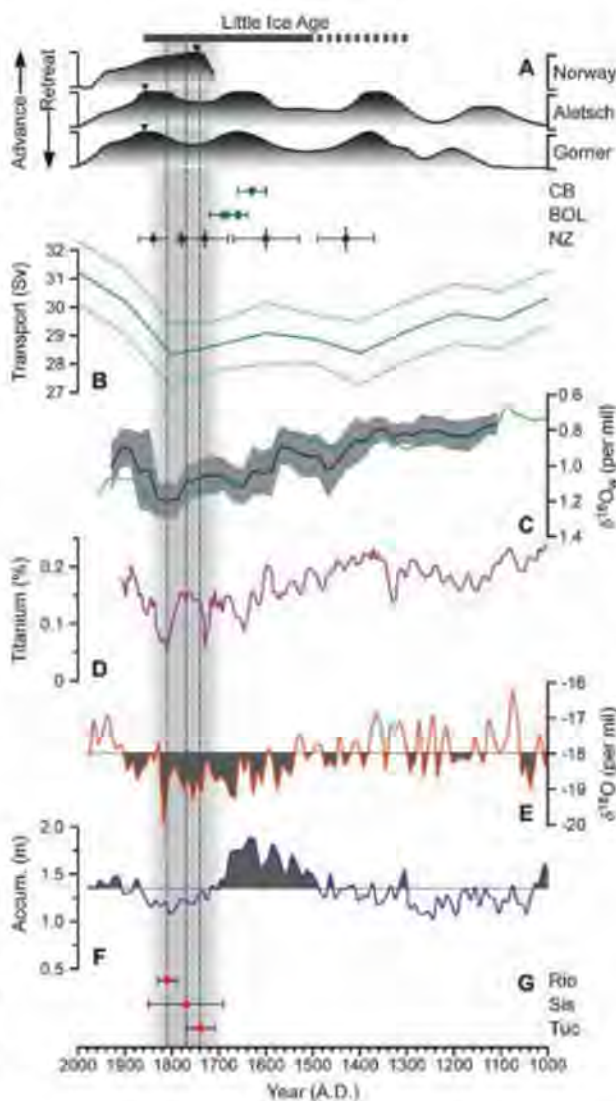


Fig. 3. Comparison of climate and proxy records spanning the last millennium. (A) Fluctuations of Nigardsbreen, Norway (23), and Great Aletsch and Gornor glaciers, Swiss Alps (24), with black triangles indicating maximum extension; lichenometrically dated glacial maxima in the Cordillera Blanca, Peru (CB) (7), and eastern Cordilleras, Bolivia (BOL) (22); ^{10}Be -dated glacial maxima in New Zealand (25), with vertical bars schematically showing decreasing amplitudes of events. (B) Volume transport of the Florida Current (27). (C) Surface water $\delta^{18}\text{O}_w$ in two Dry Tortugas cores, with higher values reflecting higher Florida Current surface salinity (26). (D) Titanium percentages in Cariaco Basin sediments, with lower values implying greater aridity in northern Venezuela and a more southerly mean latitude of the ITCZ (29). (E and F) Quelccaya Ice Cap $\delta^{18}\text{O}$ and accumulation data, with inferred colder and wetter intervals shaded in gray (8). (G) Glacial maxima from this study.

instrumental data, and proxy climate indicators. The LIA maximum occurred across Europe within the past 500 years, but records show asynchronous maxima in Scandinavia (~C.E. 1750) (23) and the Swiss Alps (~C.E. 1860) (24). The ^{10}Be -dated culminations in the Cordillera Vilcabamba show similar timing and temporal variability and support broad coherency between glacier maxima in the tropical Andes and in Europe during the late LIA. In contrast, a high-resolution ^{10}Be chronology of Holocene glacier fluctuations in the Southern Alps of New Zealand (25) reveals that the dominant glacial event of the last millennium occurred around C.E. 1400 and was followed by several more pulses before the final termination, highlighting a marked difference with the Peruvian record and implying a complex global pattern of glacial events during the LIA period.

Several paleolimnological indices of tropical Andean paleoclimate show the early Holocene to be relatively warm and arid, with drought peaking earlier near the equator and progressively later in the southern tropics (10). Sediment core proxy data from Lake Titicaca, whose hydrologic balance is diagnostic of precipitation patterns across a wide swath of tropical South America (9), indicate a lake level rise to overflow conditions between 10 to 8.5 ka, followed by a sharp drop and ensuing period of desiccation. These lake level trends agree closely with the timing of early Holocene Vilcabamba glacial culminations (Fig. 2). High lake stands and expanded glaciers were probably maintained by some combination of lower temperatures and higher precipitation, but the relative importance of temperature versus precipitation controls is unclear. Overflowing lake levels at Lake Titicaca likely reflect enhanced moisture delivery via prevailing easterly flow across the Amazon Basin (9), and we similarly hypothesize that Vilcabamba glaciers were sustained by an overall increase in snowfall, humidity, and/or cloudiness at high elevations during the early Holocene. The underlying cause of this hydrologic variability has been attributed to past fluctuations in tropical Atlantic sea surface temperatures (SST) and their impact on precipitation patterns in Amazonia, with high levels of Lake Titicaca promoted by anomalously low Atlantic SSTs and vice versa (9). We speculate that Atlantic forcings may also have played a prominent role in early Holocene Vilcabamba glacier fluctuations.

For the past millennium, it is instructive to compare the Vilcabamba glacial record to regional climate indices from the Quelccaya Ice Cap 250 km southeast of our study area (8). Low $\delta^{18}\text{O}$ and high electrical conductivity from ~C.E. 1500 to 1900 in Quelccaya ice cores are interpreted to reflect lower temperatures and increased wind velocities corresponding to the LIA, whereas ice accumulation data show a wet phase from C.E. 1500 to 1720 followed by dry conditions from C.E. 1720 to 1860 (Fig. 3). The

ages of the Vilcabamba inner moraines fall within the latter dry period, possibly signifying that glacier buildup during the wet phase was followed by a delayed onset of retreat in response to gradual moisture starvation under sustained cold conditions. A complementary perspective comes from proxy data in marine sediment cores off Peru at ~12°S and ~14°S (11), which show an abrupt shift toward the modern regime of nutrient-rich, oxygen-depleted waters around C.E. 1820 and a coeval transition from wetter to drier conditions on the western slopes of the Andes. The apparent coincidence of these shifts in the marine-based proxies with the latest LIA culmination in our Vilcabamba glacial record suggests that oceanic and terrestrial systems at these latitudes were influenced by a common climate forcing toward the end of the LIA.

Plausible climate drivers must be in accord with the occurrence of early Holocene glacial events and only slightly less extensive LIA glacial culminations during relative maxima and minima in precessional wet-season insolation, respectively (Fig. 2). For the latest Holocene, we postulate that migration of the Atlantic Intertropical Convergence Zone (ITCZ) may explain concurrent glaciations in tropical South America and northern high latitudes. Proxy data from the Florida Straits (26, 27) indicate a reduction in Gulf Stream strength during the LIA, possibly leading to decreased northward oceanic heat transport and cooling of the North Atlantic (Fig. 3). This cooling may have altered cross-equatorial SST gradients and caused southward migration of the ITCZ (28). Mineralogic data from the Cariaco Basin (29) provide evidence for a southerly excursion of the ITCZ during the LIA, lending credence to this scenario. We envision cold conditions in the north promoting European glacier expansions while a south-shifted ITCZ simultaneously brought increased glacier-nourishing snowfall to the Peruvian Andes. Subsequent northward migration of the ITCZ in step with North Atlantic warming at the close of the LIA would diminish high-elevation snowfall in the southern tropics and trigger glacier retreat in both regions. This hypothesis is consistent with the Quelccaya ice core record (8), which suggests that a reduction in regional snow accumulation preceded the retreat of Vilcabamba glaciers toward the end of the LIA (27) (Fig. 3).

A more thorough exploration of global-scale Holocene climate drivers will require testing with coupled ocean-atmosphere model simulations, but the advancement of these models depends on regional calibration with reliable paleoclimate data. Tropical glacier chronologies hold tremendous potential for this approach, and our results demonstrate that the new generation of ^{10}Be data has attained the precision necessary for reconstructing high-resolution records throughout the Holocene and up to the present day.

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Materials and Methods

Figs. S1 to S4

Tables S1 and S2

References

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Chloroquine Transport via the Malaria Parasite's Chloroquine Resistance Transporter

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The emergence and spread of chloroquine-resistant *Plasmodium falciparum* malaria parasites has been a disaster for world health. Resistance is conferred by mutations in the Chloroquine Resistance Transporter (PfCRT), an integral membrane protein localized to the parasite's internal digestive vacuole. These mutations result in a marked reduction in the accumulation of chloroquine (CQ) by the parasite. However, the mechanism by which this occurs is unclear. We expressed both wild-type and resistant forms of PfCRT at the surface of *Xenopus laevis* oocytes. The resistant form of PfCRT transported CQ, whereas the wild-type protein did not. CQ transport via the mutant PfCRT was inhibited by CQ analogs and by the resistance-reverser verapamil. Thus, CQ resistance is due to direct transport of the drug via mutant PfCRT.

Malaria, an infectious disease that is prevalent throughout the tropics, was once readily treatable by chloroquine (CQ), a drug that was cheap, safe, and effective. CQ resistance is mediated by the *Plasmodium falciparum* Chloroquine Resistance Transporter (PfCRT) (1, 2) and is associated with a marked reduction in CQ accumulation by the parasite (3, 4). CQ is a diprotic weak base (pK_a of 8.1 and 10.2, where K_a is the acid dissociation constant), with the relative proportions of the neutral, mono-protonated (CQH^+), and di-protonated (CQH_2^{2+}) species varying with pH (table S1). The neutral species enters the parasite and its internal compartments via simple diffusion. When the base enters the acidic environment of the parasite's digestive vacuole [$pH \sim 5$ (5–8)], the equilibrium is shifted toward the CQH_2^{2+} species, which is unable to diffuse across the membrane and becomes trapped, thereby accumulating to high concentrations within this compartment. CQ is thought to exert its antimalarial effect here by interfering with the detoxification of heme, which is released as a byproduct of hemoglobin digestion.

The key resistance-conferring mutation in PfCRT is the replacement of a lysine (K) with a threonine (T) at position 76 (9). This K76T mutation occurs in a region of the protein that is predicted to be involved in substrate recognition (10). It is never found in isolation, but is always accompanied by a number of what are thought to be compensatory mutations in the protein (11). We compared the function of mutant PfCRT from the CQ-resistant (CQR) *P. falciparum* strain Dd2 with that of wild-type PfCRT from the CQ-sensitive (CQS) strain D10 (fig. S1).

The digestive vacuole is a lysosomal organelle, and the targeting of PfCRT to this compartment is likely to be mediated by discrete endosomal-lysosomal trafficking motifs. Upon expression of PfCRT in *Xenopus* oocytes, such motifs may cause the protein to be targeted to analogous organelles, rendering direct measurements of PfCRT function impractical. We therefore identified and removed multiple putative trafficking motifs from both termini of the PfCRT protein sequence (fig. S1). In addition, the PfCRT coding sequence for expression in *Xenopus* oocytes was codon-harmonized to facilitate correct folding of the protein (12, 13). Hemagglutinin (HA)-tagged forms of this modified version of the PfCRT sequence were expressed in *Xenopus* oocytes, and localization of the CQS and CQR forms of PfCRT (PfCRT^{CQS} and PfCRT^{CQR}, respectively) to the oocyte plasma membrane was confirmed (Fig. 1 and fig. S2, A and B) (14).

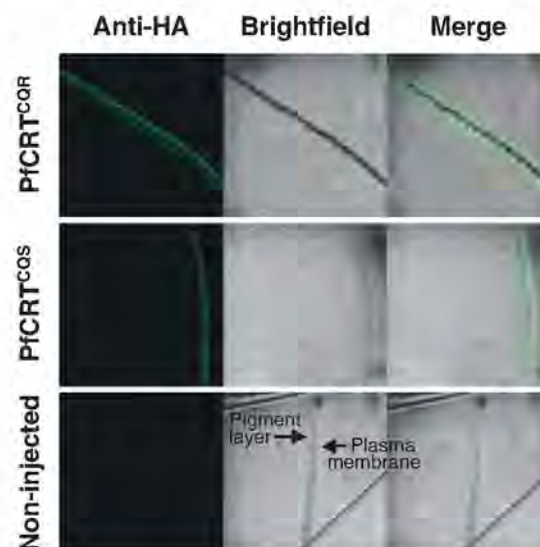
The successful expression of (motif-free, codon-harmonized) PfCRT at the oocyte surface enabled us to investigate the transport activity of the protein. Except where specified otherwise,

uptake of [³H]CQ was measured in an acidic medium ($pH = 6.0$), in which the majority of CQ was protonated. Oocytes expressing PfCRT^{CQR} showed a marked (typically 5-fold, and up to 10-fold) increase in [³H]CQ uptake relative to non-injected controls and to oocytes expressing PfCRT^{CQS} (Fig. 2A). This is consistent with PfCRT^{CQR}, but not PfCRT^{CQS}, mediating the transport of [³H]CQ. (The membrane potential and cytosolic pH in PfCRT^{CQR}-expressing oocytes were the same as those in PfCRT^{CQR}-expressing oocytes; table S2.) In contrast, oocytes injected with complementary RNA (cRNA) encoding native (that is, motif-replete, nonharmonized) PfCRT^{CQR} did not show increased [³H]CQ uptake, nor was the protein present at significant levels in the plasma membrane (fig. S3, A and B). The sequence modifications made here therefore facilitated the functional expression of PfCRT.

T76K and S163R (15) mutations in PfCRT^{CQR} restore CQ sensitivity to CQR parasites (9, 16). The introduction of either one of these changes to PfCRT^{CQR}, each of which entailed the addition of a positive charge to the putative substrate-binding site of the protein (10, 11), resulted in the loss of CQ transport activity (Fig. 2B). In contrast, the introduction of K76T to PfCRT^{CQS} did not result in a significant increase in [³H]CQ uptake (Fig. 2B). (PfCRT^{CQS} K76T did localize to the oocyte plasma membrane; fig. S4.) The K76T mutation is therefore necessary but not sufficient for the transport of CQ via PfCRT. This is consistent with the other PfCRT mutations acting in synergy with K76T to confer CQ resistance.

CQ transport showed a strong dependence on the pH of the medium (Fig. 2C). Under alkaline conditions, [³H]CQ was taken up to similarly high levels in noninjected oocytes and oocytes expressing PfCRT^{CQR} or PfCRT^{CQS}. This is likely to represent simple diffusion of uncharged CQ (uptake was nonsaturable at $pH = 7.4$ and 8.4 ; fig. S5). In contrast, at $pH = 5.0$ to 6.9 , CQ transport in oocytes expressing PfCRT^{CQR} was much higher than that in noninjected oocytes or

Fig. 1. Immunolocalization of PfCRT in the *Xenopus* oocyte. The oocyte plasma membrane lies over a band of granules known as the pigment layer. This, in turn, surrounds a cytoplasm crowded with yolk sacs and small endosomal- and lysosomal-type organelles (23). Expression of C-terminally HA-tagged PfCRT^{CQR} or PfCRT^{CQS} results, in each case, in the appearance of a fluorescent band external to the pigment layer, indicating that both proteins are expressed in the oocyte plasma membrane. The band is not present in noninjected oocytes. Similar results were obtained with N-terminally tagged PfCRT (fig. S2A).



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oocytes expressing PfCRT^{COS} [$P < 0.05$, analysis of variance (ANOVA)], with the maximum difference (that is, the pH optimum for PfCRT^{COR}-mediated CQ transport) observed at pH = 6.0 (fig. S6). This pH dependence is consistent with CQ being transported in its mono- or di-protonated forms. Indeed, depolarization of the membrane potential by the replacement of extracellular Na⁺ with K⁺ (at pH = 6.0; table S3) resulted in a $25 \pm 2\%$ reduction in PfCRT^{COR}-mediated CQ transport (Fig. 2D; $P < 0.005$, paired t test). The decrease in PfCRT^{COR}-mediated CQ transport as pH was reduced from 6.9 to 5.5 (Fig. 2C) may have been due, at least in part, to the oocyte membrane po-

tential undergoing a depolarization over the same pH range (table S2).

The uptake of [³H]CQ via PfCRT^{COR} decreased with increasing concentrations of unlabeled CQ (Fig. 2E), which is consistent with a saturable transport mechanism. In contrast, raising the concentration of unlabeled CQ had little effect on [³H]CQ transport in PfCRT^{COS}-expressing and noninjected oocytes. This is consistent with the entry of the drug into these oocytes being via simple diffusion of the neutral species. A least-squares fit of the data to the Michaelis-Menten equation yielded an apparent Michaelis constant $K_M(\text{CQ})$ of $245 \pm 3 \mu\text{M}$ and a maximum velocity

V_{max} of $67 \pm 13 \text{ pmol hour}^{-1}$ per oocyte (Fig. 2E, inset) for the transport of CQ via PfCRT^{COR}. (The presence of a high extracellular concentration of CQ did not affect the membrane potential or cytosolic pH of noninjected PfCRT^{COS}- or PfCRT^{COR}-expressing oocytes; table S4.)

Verapamil increases the accumulation of CQ by resistant parasites in vitro and thereby increases their sensitivity to CQ (4). Verapamil inhibited the transport of CQ via PfCRT^{COR} (Fig. 2F and Table 1; half-maximum inhibitory concentration $\text{IC}_{50} = 30 \pm 3 \mu\text{M}$), as did a range of quinolines including quinine and amodiaquine (table S5). In contrast, piperazine and artemisinin (both clin-

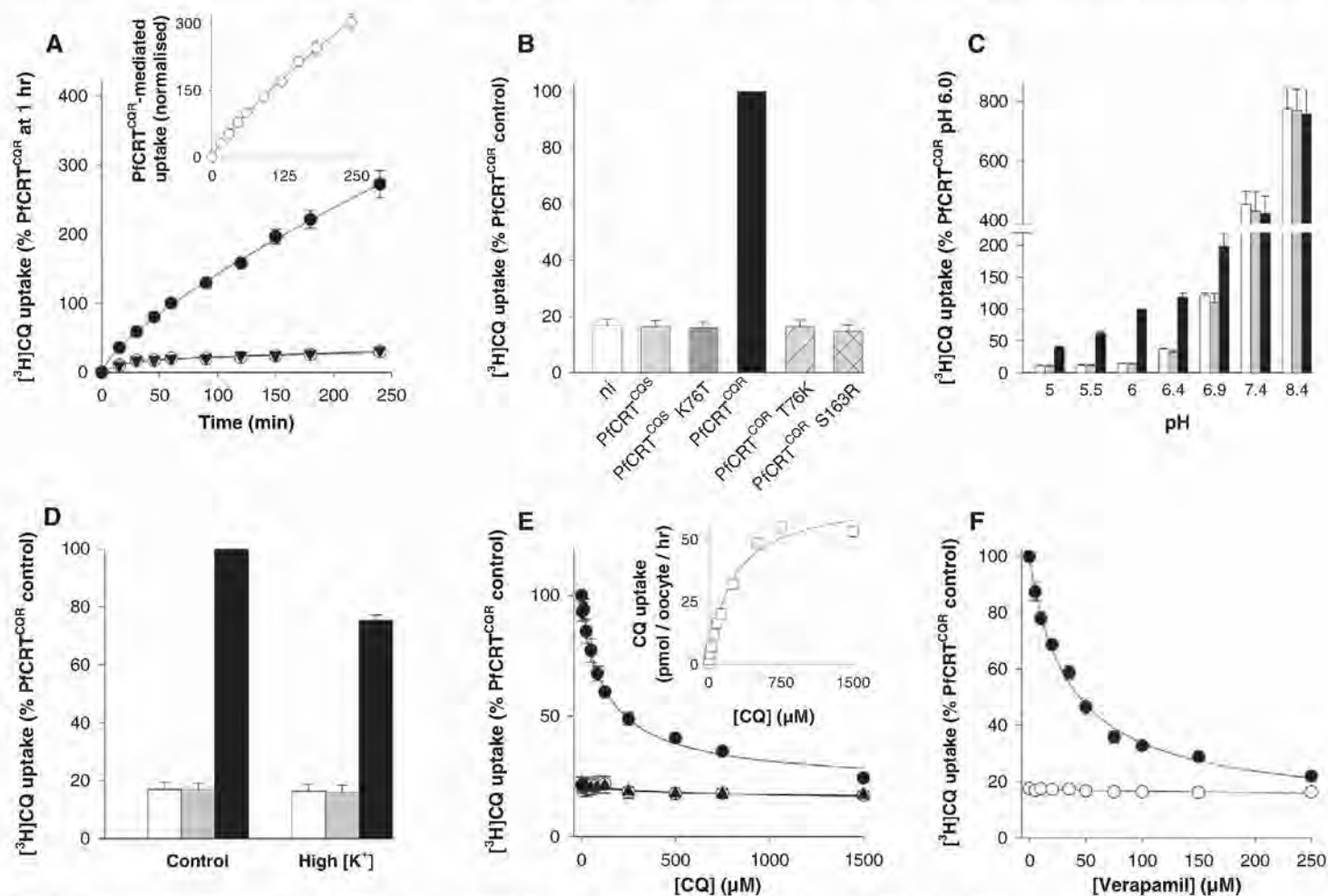


Fig. 2. Transport properties of PfCRT^{COR} in *Xenopus* oocytes. (A) Oocytes expressing PfCRT^{COR} (solid circles) showed a marked increase in CQ transport relative to noninjected oocytes (solid triangles) and oocytes expressing PfCRT^{COS} (open circles). Rates of CQ uptake (pmol hour⁻¹ per oocyte; $n = 3 \pm \text{SEM}$, estimated from uptake at 60 min) were as follows: noninjected, 1.14 ± 0.16 ; PfCRT^{COS}, 1.14 ± 0.19 ; and PfCRT^{COR}, 5.54 ± 0.44 . The PfCRT^{COR}-mediated uptake of [³H]CQ (obtained by subtracting uptake in oocytes expressing PfCRT^{COS} from that in PfCRT^{COR}-expressing oocytes) was approximately linear with time for at least 4 hours (inset). (B) Introduction of K76T to PfCRT^{COS} did not increase CQ transport to above that measured in oocytes expressing PfCRT^{COS} or in noninjected (ni) oocytes ($P > 0.05$, ANOVA). The introduction of T76K or S163R to PfCRT^{COR} resulted in the loss of PfCRT^{COR}-associated CQ transport ([³H]CQ uptake in these oocytes did not differ significantly from that in noninjected oocytes or from oocytes expressing PfCRT^{COS}; $P > 0.05$, ANOVA). (C) pH dependence of [³H]CQ uptake into noninjected oocytes (white bars), oocytes expressing PfCRT^{COS} (gray bars) and oocytes expressing PfCRT^{COR} (black

bars). (D) Effect of depolarization of the oocyte plasma membrane (by replacement of Na⁺ with K⁺ in the extracellular medium) on [³H]CQ uptake into noninjected oocytes (white bars), oocytes expressing PfCRT^{COS} (gray bars), and oocytes expressing PfCRT^{COR} (black bars). PfCRT^{COR}-expressing oocytes, but not PfCRT^{COS}-expressing or noninjected oocytes, showed a significant decrease in CQ uptake when depolarized [$P < 0.005$ and $P > 0.05$ (ANOVA), respectively]. (E) Effect of unlabeled CQ on the uptake of [³H]CQ by noninjected oocytes (solid triangles) and oocytes expressing either PfCRT^{COR} (solid circles) or PfCRT^{COS} (open circles). The inset shows the [CQ]-dependence of PfCRT^{COR}-mediated uptake, which was calculated by subtracting the uptake measured in oocytes expressing PfCRT^{COS} from that in oocytes expressing PfCRT^{COR} at each CQ concentration. (F) Inhibition by verapamil of the uptake of [³H]CQ by oocytes expressing PfCRT^{COR} (solid circles) or PfCRT^{COS} (open circles). In all panels, uptake is shown as mean $\pm$ SEM from three to five separate experiments, within which measurements were made from 10 oocytes per treatment.

Table 1. IC₅₀ values for the inhibition of PfCRT^{CQR}-mediated CQ transport by a number of drugs and peptides. PfCRT^{CQR}-mediated CQ transport was calculated by subtracting the uptake measured in oocytes expressing PfCRT^{CQS} from that in oocytes expressing PfCRT^{CQR}. The data are shown in fig. S7 and Fig. 2F. IC₅₀ values were derived by least-squares fit of the equation $Y = Y_{\min} + [(Y_{\max} - Y_{\min}) / (1 + ([\text{inhibitor}] / \text{IC}_{50})^C)]$, where Y is PfCRT^{CQR}-mediated CQ transport, $Y_{\min}$ and $Y_{\max}$ are the minimum and maximum values of Y , and C is a constant. All values are mean $\pm$ SEM from $n = 3$ or 4 separate experiments, within which measurements were made from 10 oocytes per treatment.

Compound	IC ₅₀ (μM)
Verapamil	30 $\pm$ 3 ($n = 4$)
Quinine	48 $\pm$ 6 ($n = 3$)
Amantadine	770 $\pm$ 63 ($n = 3$)
YPWF-NH ₂ (endomorphin-1)	64 $\pm$ 5 ($n = 3$)
WHWLQL (α_1 -mating factor peptide)	99 $\pm$ 9 ($n = 3$)
VVYPWTQR (a hemoglobin peptide)	363 $\pm$ 28 ($n = 4$)
RPPGFSPFR (Bradykinin)	1095 $\pm$ 71 ($n = 3$)

ically effective against both CQS and CQR parasites) had no effect. Amantadine exhibits some antimalarial activity in vitro, particularly against CQR parasites (16), and also inhibited transport via PfCRT^{CQR} (table S5).

Several peptides were found to cause a pronounced inhibition of CQ transport via PfCRT^{CQR} (table S5). Most of the peptides that are active against PfCRT^{CQR} have key elements of the CQ-resistance reverser pharmacophore [hydrogen bond acceptor and two hydrophobic aromatic rings (17)] (table S6). This pharmacophore can be viewed as defining the basic elements involved in interactions between PfCRT^{CQR} and substrates or inhibitors.

The concentration dependence of inhibition of CQ transport was determined for a number of compounds (Table 1 and fig. S7). YPWF-NH₂ (endomorphin-1; an opioid receptor agonist) was the most effective peptide inhibitor of PfCRT^{CQR}-mediated CQ uptake, with an IC₅₀ comparable to that of quinine and verapamil. Measurements of [³H]YPWF-NH₂ uptake in oocytes expressing different PfCRT constructs revealed that PfCRT^{CQR}, but not PfCRT^{CQR}-T76K, PfCRT^{CQR}-S163R, or PfCRT^{CQS}, mediates the transport of this peptide (fig. S8).

We have demonstrated the transport of CQ via mutant PfCRT, which provides an explanation for the phenomenon of CQ resistance, as well as for the reversal of CQ resistance by reversing agents such as verapamil. The presence of a positive charge (K76 or R163) in the PfCRT substrate-binding site prevents CQH₂²⁺ (or CQH⁺) from interacting with the transporter. The K76T mutation removes the positive charge, altering the substrate specificity of PfCRT to allow the transport of the protonated drug. In the parasite, the presence of mutant PfCRT on the digestive vacuole will allow the protonated drug to be transported down its electrochemical gradient, out of the vacuole, and thus away from its site of action (fig. S9). This mechanism is consistent with recent studies implicating PfCRT^{CQR} in the transport of [³H]CQ in CQR parasites (18–20) and in *Dictyostelium discoideum* transformants expressing PfCRT at endosomal membranes (21). It is also consistent with the recent demonstration of a (verapamil-

sensitive) CQ-mediated efflux of H⁺ from the digestive vacuole of CQR parasites (22). The achievement of a robust expression system for PfCRT has the potential to facilitate the rational design of novel CQ-like drugs that bypass the resistance mechanism and/or the design of clinically effective resistance-reversing agents.

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Supporting Online Material

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Figs. S1 to S9

Tables S1 to S6

References

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Global Analysis of Cdk1 Substrate Phosphorylation Sites Provides Insights into Evolution

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To explore the mechanisms and evolution of cell-cycle control, we analyzed the position and conservation of large numbers of phosphorylation sites for the cyclin-dependent kinase Cdk1 in the budding yeast *Saccharomyces cerevisiae*. We combined specific chemical inhibition of Cdk1 with quantitative mass spectrometry to identify the positions of 547 phosphorylation sites on 308 Cdk1 substrates in vivo. Comparisons of these substrates with orthologs throughout the ascomycete lineage revealed that the position of most phosphorylation sites is not conserved in evolution; instead, clusters of sites shift position in rapidly evolving disordered regions. We propose that the regulation of protein function by phosphorylation often depends on simple nonspecific mechanisms that disrupt or enhance protein-protein interactions. The gain or loss of phosphorylation sites in rapidly evolving regions could facilitate the evolution of kinase-signaling circuits.

Cyclin-dependent kinases (Cdks) drive the major events of the eukaryotic cell-division cycle (1). Comprehensive identification and analysis of Cdk substrates would enhance our understanding of cell-cycle control

and provide insights into the mechanisms and evolution of regulation by phosphorylation. We therefore developed methods for comprehensive identification of the sites of Cdk1 phosphorylation on large numbers of substrates in vivo. We

used quantitative mass spectrometry to identify sites at which phosphorylation decreased *in vivo* after specific inhibition of Cdk1 (2). We used stable isotope labeling of amino acids in culture (SILAC) in the *cdk1-as1* yeast strain, in which Cdk1 is replaced with a mutant protein engineered to be specifically and rapidly inhibited by the pyrimidine-based inhibitor 1-NM-PP1 (3). Cells of a *cdk1-as1; arg4Δ; lys1Δ* strain, which require exogenous lysine and arginine to survive, were grown in medium containing lysine and arginine (the “light” culture) or in medium supplied with arginine and lysine labeled with stable heavy isotopes of carbon and nitrogen (^{13}C and ^{15}N) (fig. S1). This “heavy” culture was treated briefly (15 min) with 10 μM 1-NM-PP1 to inactivate Cdk1-as1. The cultures were then mixed together, lysed, and subjected to trypsinization. Phosphopeptides were purified from the peptide mixture and analyzed by means of tandem mass spectrometry (MS/MS). The precise sites of phosphorylation were inferred from the mass signature of peptide ion fragments in MS/MS spectra, and the ratio of heavy to light phosphopeptide in the MS spectra was used to infer relative abundance of all phosphopeptides with and without Cdk1 inhibition. We analyzed three different cell populations: an asynchronous population; a culture arrested in mitosis with the spindle poison nocodazole; and a culture arrested in late mitosis by overexpression of a nondegradable cyclin, Clb2- ΔN (2).

We collected 354,560 MS/MS spectra, of which 74,093 were successfully matched to phosphopeptide sequences. In total, we identified 10,656 different phosphorylation sites (database S1), of which 8710 sites on 1957 proteins were assigned a precise position with >95% confidence (database S2). The $\log_2$ heavy/light (H/L) ratios for nonphosphopeptides were tightly distributed around zero (a 1:1 ratio), indicating that global protein abundance was not affected by brief Cdk1 inhibition, whereas the $\log_2$ H/L ratios for phosphopeptides were more broadly distributed (Fig. 1A; see database S2 for a list of H/L ratios). A leftward shift in the H/L ratio of a phosphopeptide indicates that the abundance of that phosphopeptide decreased when Cdk1 was inhibited, as was expected for Cdk1 substrates. Indeed, we observed a leftward shift in peptides phosphorylated at a Cdk1 consensus sequence (S/T*-P, or S/T*-P-x-K/R, where x represents any amino acid and the asterisk indicates the site of phosphorylation), and the phosphopeptides with the lowest H/L ratios ($\log_2$ H/L < -3) were enriched for the Cdk1 consensus site (Fig. 1B), indicating that

peptides whose phosphorylation decreased most after Cdk1 inhibition were enriched for direct targets of Cdk1. We therefore used two criteria to define a phosphorylation site as a Cdk1 substrate. First, the phosphorylated serine or threonine must be followed by a proline so as to conform to the minimal Cdk1 consensus sequence. Second, the phosphopeptide must decline in abundance by at least 50% after Cdk1 inhibition (as indicated by $\log_2$ H/L < -1) in one or more of our three experiments. Based on this double filtering, 547 distinct phosphorylation sites were identified on 308 candidate Cdk1 substrates (Fig. 1C and tables S1 and S2, substrate list).

Phosphorylation of Cdk1 consensus sites was observed on 67% (122 of 181) of proteins previously identified as Cdk1 substrates *in vitro* (4).

Sixty-six percent (80 of 122) of these proteins contained sites at which phosphorylation decreased ($\log_2$ H/L < -1) after inhibition of Cdk1 (only 45 of 122 are expected if there is no correlation between the experiments *in vitro* and *in vivo*; χ^2 test, $P < 10^{-10}$).

A gene ontology analysis of the candidate substrates revealed a strong enrichment for cell cycle-related functional categories (such as GO:0007049, Cell Cycle; hypergeometric $P < 10^{-20}$) (table S3). Substrates are also involved in processes that are not traditionally thought of as being under cell-cycle control, including translation, chromatin remodeling, protein secretion, and nuclear transport (Fig. 2).

To modulate protein function, addition of a phosphate at a specific site can drive a precise

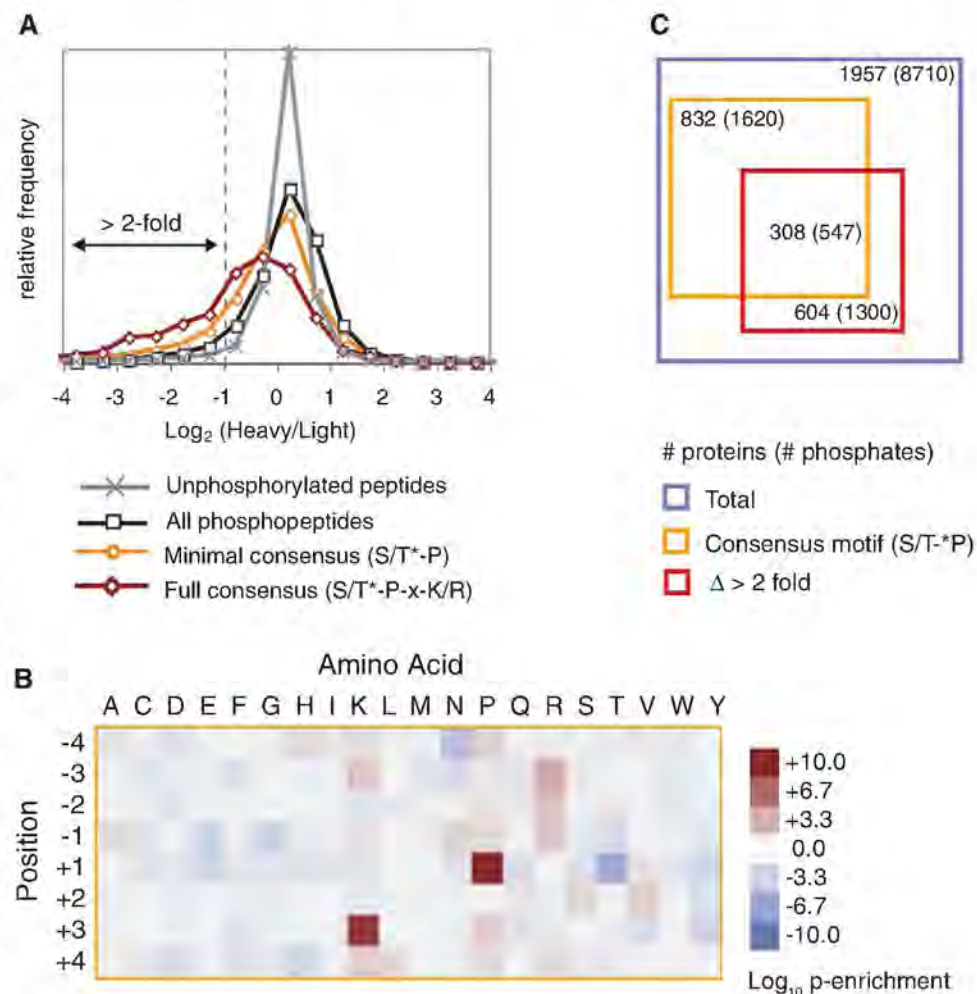


Fig. 1. Large-scale identification of Cdk1 substrates *in vivo*. **(A)** Distributions of $\log_2$ H/L ratios for unphosphorylated peptides (gray), all phosphopeptides (black), and phosphopeptides containing a minimal (orange) or full (red) Cdk1 consensus phosphorylation motif. **(B)** $\log_{10}$ P values (binomial distribution) for the enrichment (red) or depletion (blue) of each amino acid (columns) at each position flanking the phosphorylated serine or threonine (rows) in phosphopeptides that changed greatly in abundance ($\log_2$ H/L < -3) relative to residues flanking serines and threonines proteome-wide. **(C)** Venn diagram representing the number of proteins and unique phosphorylation sites identified in the three experiments (2). The blue square indicates the total number of proteins and phosphorylation sites for which H/L ratios could be rigorously determined and for which the precise position of the phosphate could be assigned with 95% confidence. The orange square indicates proteins and phosphopeptides containing a minimal consensus motif, and the red square indicates proteins and phosphopeptides that decreased in abundance by over 50% after Cdk1 inhibition ($\log_2$ H/L < -1). Cdk1 substrates (table S1) were defined by the overlap between the orange and red squares. Squares are scaled to the number of proteins.

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conformational change in a protein loop or domain, thereby altering its activity or its interactions with other proteins (fig. S2A). This mechanism generally relies on coordination of the phosphate by networks of hydrogen bonds and is therefore highly context-dependent and unlikely to arise by a small number of random mutations. Alternatively, the addition of phosphates to a protein surface can directly disrupt interactions with other proteins (5, 6) or can generate new interactions with phosphopeptide-binding modules such as 14-3-3, polo-box, WW, and Src homology 2 do-

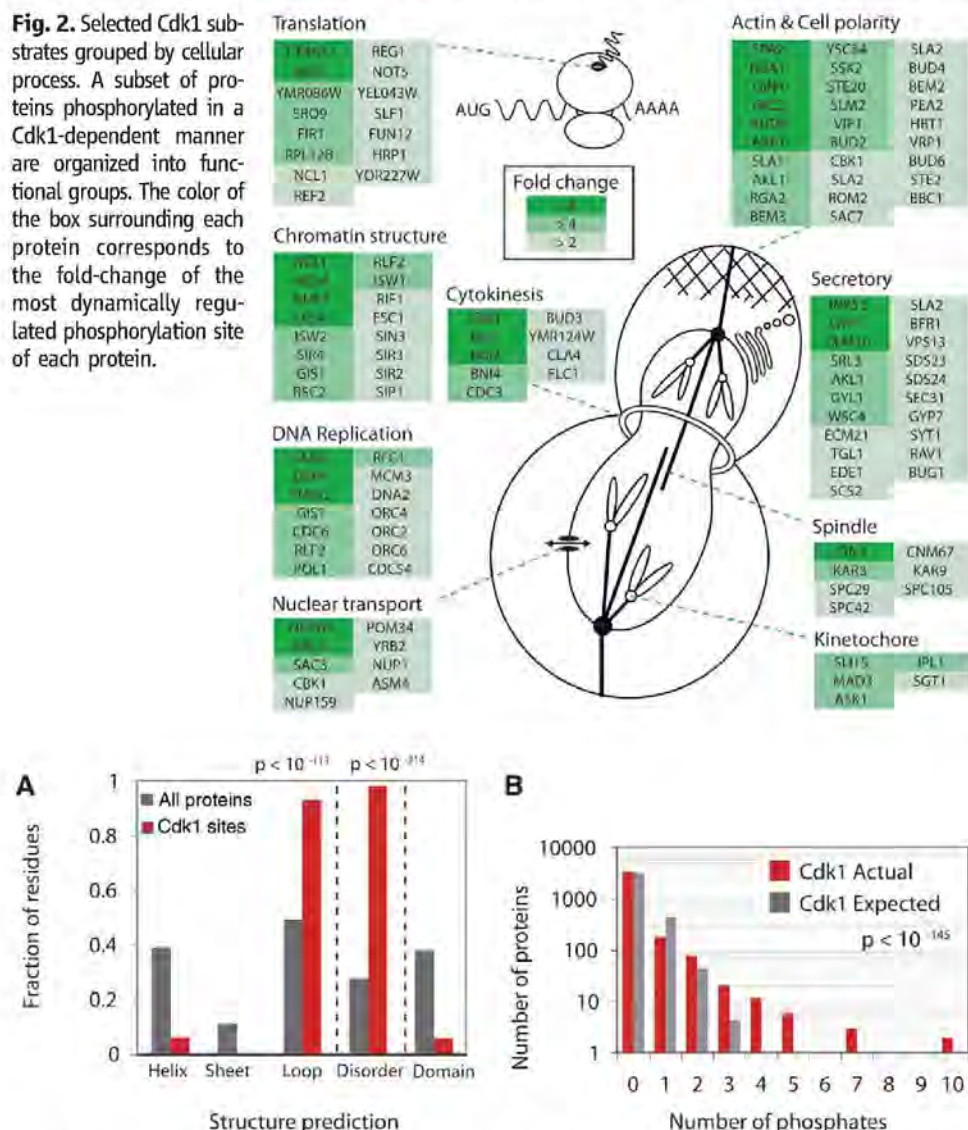
main (fig. S2B) (7, 8). In these cases, the position of the phosphate (or phosphates) is less context-dependent and therefore less constrained, and this form of phosphoregulation is expected to arise more readily through random mutation.

To assess the relative importance of these regulatory mechanisms in Cdk1 function, we analyzed the structural context and conservation of the 547 Cdk1-dependent phosphorylation sites. We found that more than 90% of these sites are predicted to be in loops and disordered regions (Fig. 3A and table S4), which is consistent with

previous analyses of phosphorylation sites in general (9). Furthermore, we found that many Cdk1 targets have a greater number of phosphates than would be expected by chance ($P < 10^{-145}$; median Mann-Whitney P value from comparison of true distribution to 1000 simulations) (Fig. 3B), indicating that Cdk1 substrates tend to be phosphorylated at multiple sites. We also found that Cdk1-dependent phosphorylation sites tend to cluster in the primary amino acid sequence ($P < 10^{-15}$; median Mann-Whitney P value from comparison of true distribution to 1000 simulations) (Fig. 3C), suggesting that multiple phosphorylations modulate the same protein surface.

We used the complete genome sequences of 32 fungal species (fig. S3) to examine the evolution of Cdk1 phosphorylation sites. For each Cdk1 substrate, orthologous sequences were identified and aligned (10, 11). A representative short stretch of alignment from the protein Shp1 is illustrated in Fig. 4A. This region of Shp1 contains two experimentally identified phosphorylation sites with different evolutionary dynamics. The precise position of site A, which lies on the edge of a predicted folded domain, has been preserved throughout the lineage. In contrast, the position of site B, which lies in a predicted disordered region, is conserved only in the closely related *sensu stricto* *Saccharomyces* group. However, Cdk1 consensus sites are found at other positions in this region throughout the lineage. Thus, although phosphorylation in the disordered region appears to be conserved, the precise position of the sites is less constrained.

Hierarchical clustering of all 547 Cdk1 phosphorylation sites showed that relatively few exhibit strong evolutionary conservation of their



precise position (Fig. 4B, top, red box, and fig. S4). These phosphorylations might be expected to drive precise conformational changes and might therefore evolve more slowly (fig. S2A). Indeed, this type of substrate is highly enriched for metabolic enzymes (hypergeometric $P = 0.001$ for metabolic enzymes with precise-position age more than 0.5 units greater than enrichment age), which are generally more ancient than other open reading frames (ORFs) (fig. S5) and therefore might have evolved this form of regulation long ago.

A larger number of phosphorylation sites showed a different behavior: The precise position of the phosphorylation was conserved only in very closely related species, but there was a statistically significant enrichment of consensus sites throughout the lineage (Fig. 4B, bottom,

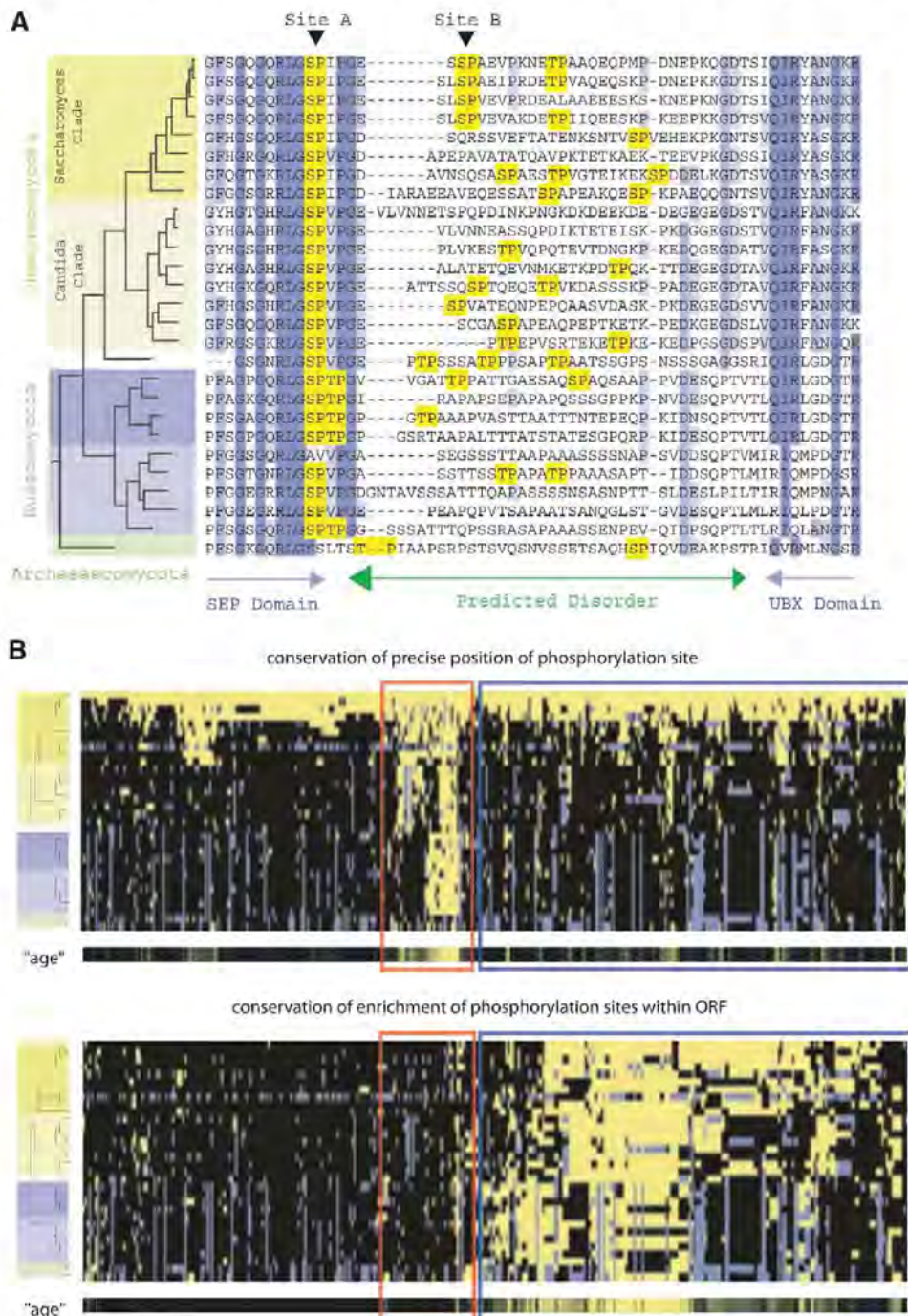
blue box, and table S5). This pattern of evolution is consistent with context-independent forms of regulation, as discussed above (fig. S2B).

Precise phosphorylation site positioning might not be required for regulation of a protein by interactions with phosphopeptide-binding domains. We found a highly significant overlap between Cdk1 substrates and the binding partners of the phosphopeptide-binding domain found in 14-3-3 proteins. *S. cerevisiae* has two 14-3-3 proteins, Bmh1 and Bmh2. Ninety-four of 278 Bmh1- or Bmh2-interacting proteins (12) were identified as Cdk1 substrates in our studies (hypergeometric $P < 1 \times 10^{-20}$, assuming 3838 total ORFs) (fig. S6A). 14-3-3 proteins typically act as dimers and therefore contain two phosphate-binding sites that bind with higher affinity to

multiphosphorylated proteins (13). Indeed, substrates that interact with Bmh1 and Bmh2 were more likely to be enriched with multiple Cdk1 consensus sites (Mann-Whitney $P < 10^{-4}$) (fig. S6B). Thus, shifting multisite phosphorylation might act in some cases to create generic interactions with phosphate-binding domains.

Several established Cdk substrates are regulated in multiple species by multisite phosphorylation in rapidly evolving regions (table S6). For example, clusters of Cdk1 phosphorylation sites in components of the prereplicative complex vary in position during evolution but are still likely to confer the same regulation (14–16). Our work reveals that many Cdk1 substrates are phosphorylated in vivo at rapidly evolving site clusters, which are likely to modify substrate func-

Fig. 4. Evolution of Cdk1-dependent phosphorylation sites. **(A)** Representative multiple sequence alignment of 27 orthologs of *S. cerevisiae* Shp1. The ascomycete phylogeny (fig. S3) is shown to the left of the alignment. Amino acid conservation is indicated by blue boxes, and minimal Cdk1 consensus motifs are highlighted in yellow. Blue arrows indicate predicted domains, and the green arrow indicates a predicted disordered region (PONDR). **(B)** Hierarchical clusters summarize the evolution of all 547 Cdk1 phosphorylation sites: Each row is a different species, and each column is a different phosphorylation site. The phylogeny (32 species) (fig. S3) is represented by a tree at the left. In the top clustergram, yellow indicates that a consensus site (S/T-P) aligns with the phosphorylation site detected in *S. cerevisiae* (top row). Gray indicates that no single ortholog was detected in that species. In the bottom clustergram, yellow indicates that there is an enrichment of Cdk1 consensus sites in the ortholog of the *S. cerevisiae* protein that we identified as a Cdk1 substrate. Enrichment in each ortholog was assessed by assuming that the expected frequency of a consensus motif is equal to the global frequency across all ORFs in the species and then using the Poisson distribution to calculate the probability of observing greater than or equal to the actual number of consensus sites. Enrichment was defined by a P value of less than 0.01 (for example, a typical 400-residue protein is expected to contain 2.8 sites, but must contain eight or more sites to achieve $P < 0.01$) (table S5). Two groups are highlighted within the clustergrams: one with conservation of precise site position (red box) and one with conservation of enrichment of consensus sites (blue box). Beneath each clustergram is a metric termed “age,” which summarizes each column as a single conservation score (fig. S4). More intense yellow indicates greater conservation.



tion by simply disrupting or generating protein-protein interactions (fig. S2B).

An important implication of flexibility in phosphorylation site positioning is that combinatorial control by multiple kinases is readily evolved. Indeed, the protein kinase Ime2, a distant relative of Cdk1 that is expressed solely in meiotic cells, phosphorylates a large number of Cdk1 substrates at distinct sites but can still have the same effect as Cdk1 on substrate function (17).

The evolution of Cdk1 signaling appears to share features with the evolution of transcriptional regulation (fig. S7). Transcriptional regulators and Cdks both maintain their biochemical specificities (the DNA consensus motif and peptide consensus motif, respectively) over long evolutionary time scales. However, in both cases there is rapid evolution of the intergenic and disordered regions, respectively, that contain these motifs. In transcriptional regulation, DNA sequence motifs can function from many positions relative to the gene being controlled and, because of their short length and sequence degeneracy, can evolve rapidly (18–20). Similarly, many Cdk1 phosphorylation sites are not tightly

constrained within the protein target sequence, and the signals for phosphorylation are short and easily evolved. These features allow cell-cycle control mechanisms to adapt rapidly to developmental challenges and opportunities that arise over time.

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Supporting Online Material

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Positive Selection of Tyrosine Loss in Metazoan Evolution

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John Nash showed that within a complex system, individuals are best off if they make the best decision that they can, taking into account the decisions of the other individuals. Here, we investigate whether similar principles influence the evolution of signaling networks in multicellular animals. Specifically, by analyzing a set of metazoan species we observed a striking negative correlation of genomically encoded tyrosine content with biological complexity (as measured by the number of cell types in each organism). We discuss how this observed tyrosine loss correlates with the expansion of tyrosine kinases in the evolution of the metazoan lineage and how it may relate to the optimization of signaling systems in multicellular animals. We propose that this phenomenon illustrates genome-wide adaptive evolution to accommodate beneficial genetic perturbation.

It is a biological paradox that organism complexity shows limited correlation with gene repertoire size (1). However, some protein families (2) have expanded with organism complexity as measured by number of cell types (3), especially those involved in regulation, such as

tyrosine kinases in signaling, cell-cell communication, and tissue boundary formation (4, 5). We observed a striking negative correlation of genomically encoded tyrosine content with the number of distinct cell types in metazoan species (Spearman's $\rho = -0.89$, approximate $P = 3.0 \times 10^{-6}$; Pearson's $\rho = -0.89$, approximate $P = 4.0 \times 10^{-6}$) (Fig. 1A). Thus, metazoans with more cell types have proportionally less potential tyrosine phosphosites. Similarly, we observed that the number of tyrosine kinase domains correlates negatively with genomic tyrosine content (Spearman's $\rho = -0.68$, approximate $P = 3.7 \times 10^{-3}$; Pearson's $\rho = -0.81$, approximate $P = 1.3 \times 10^{-4}$) (Fig. 1B). Including dual-specificity mixed-lineage kinases (MLKs) and mitogen-activated protein kinase kinases (MEKs) revealed a similar pattern (fig. S1A).

These observations suggest an evolutionary model in which the acquisition of a tyrosine kinase results in systems-level adaptation to remove deleterious phosphorylation events that cause aberrant cellular behavior and diseases (4). Assuming that a cell begins with a single tyrosine kinase, which is subsequently duplicated, it follows that the kinases may functionally diverge, as a result of relaxation in evolutionary constraints, to phosphorylate new substrates. Emerging kinase specificities could be retained if new substrates confer selection advantage. However, it is unlikely that every new phosphorylation event is beneficial. We hypothesize that optimization of newly emerged signaling networks would follow (6) through the elimination of detrimental phosphorylation events by tyrosine-removing mutations. Even if many new phosphorylation sites are not deleterious, an organism with minimized noisy signaling systems is likely to have a fitness advantage. This scenario is repeated with the subsequent duplication of tyrosine kinases leading to more tyrosine residues lost (7).

Despite several recent systematic phosphoproteomic studies (8), many human proteins have no observed phosphotyrosines. Our model suggests that tyrosine loss had occurred predominantly in these proteins in order to minimize tyrosine phosphorylation. To test this hypothesis, we investigated differences in tyrosine loss between these proteins (Non-pTyr) and those that are tyrosine phosphorylated (pTyr). Comparing members of these two groups to their orthologous proteins in *S. cerevisiae* (7), which lack conventional tyrosine kinases, enabled us to assess the degree of tyrosine loss that may be triggered by the onset of phosphotyrosine signaling in metazoans.

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A significantly smaller fraction of amino acids are tyrosines in human proteins than in their yeast orthologs (approximate $P = 3.5 \times 10^{-4}$, paired Wilcoxon signed rank test) (Fig. 1C). However, this phenomenon was statistically more pronounced in non-pTyr proteins than in pTyr proteins (approximate $P = 5.1 \times 10^{-9}$, Mann-Whitney test) (Fig. 1C). A similar trend was observed on the basis of absolute tyrosine residue counts (approximate $P = 2.0 \times 10^{-7}$, Mann-Whitney test) (fig. S1B) and on a higher confidence subset of pTyr proteins that either have multiple phosphotyrosines or have sites observed in multiple studies (approximate $P = 1.3 \times 10^{-7}$, Mann-Whitney test).

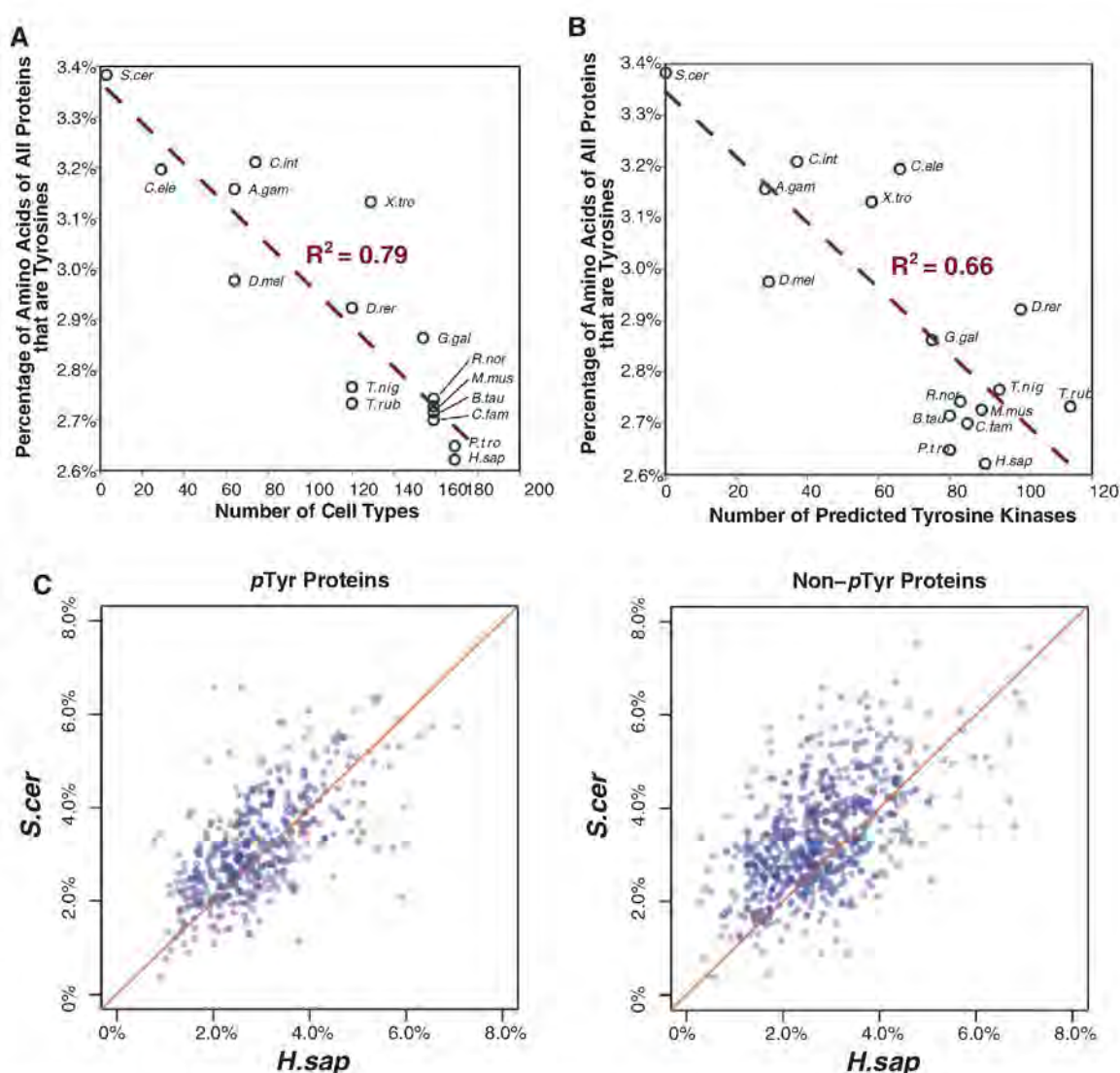
Thus, tyrosine loss was strongly favored in human protein evolution, most notably in protein subsets that are not known to be tyrosine-phosphorylated. Genetic drift (9) is unlikely to account for these differences observed in a large number of evolutionarily distant human-yeast protein orthologs. Because tyrosine is an essential

and the most expensive amino acid to biosynthesize (10) after tryptophan and phenylalanine, essentiality and biosynthetic cost could be major factors in the observed loss. However, this is unlikely because we observed a strong positive correlation of number of cell types with tryptophan and a weaker negative correlation for phenylalanine (table S1). Instead, we propose that positive selection of tyrosine-removing mutations occurred in the metazoan lineage to reduce adventitious tyrosine phosphorylation, at least in part. This optimization process probably shaped signaling networks crucial for the development of multicellular animals. Additionally, this could provide a mechanism to prevent unspecific phosphorylation events that operates with the evolution of domains, consensus motifs (11), and contextual factors to colocalize kinases with their substrates (11–13). We observed a slightly stronger negative correlation of genomically encoded tyrosine content with the number of inferred phosphotyrosine-

binding domains than tyrosine kinase domain count (Spearman's $\rho = -0.81$, Pearson's $\rho = -0.88$) (fig. S1A), which is in agreement with the notion that tyrosine phosphorylation exerts parts of its functional effects through creating binding sites for phosphobinding domains like Src homology 2 (SH2) and phosphotyrosine binding domain (PTB) (14).

The choanoflagellate *Monosiga brevicollis*, which is a member of the only known unicellular lineage with canonical tyrosine kinases (15), is an outlier in the cell-type correlation studied above. This observation is consistent with the emerging picture that choanoflagellates represent a distinct evolutionary branch from metazoans in which phosphotyrosine-signaling systems have been used for divergent functions (16, 17). Nevertheless, the *Monosiga* analysis is still consistent with optimization of phosphotyrosine signaling in this lineage; compared with the metazoans analyzed here, *Monosiga* has higher numbers of tyrosine kinases

Fig. 1. Correlation of expansion of phosphotyrosine-signaling systems with loss of genome-encoded tyrosine residues. **(A)** The genomically encoded tyrosine content in metazoan organisms and yeast correlate negatively and significantly with organism complexity as measured by distinct cell types (2). Bakers' yeast (*S. cerevisiae*) is included as a unicellular eukaryote for comparison. The species analyzed are yeast (*S. cerevisiae*), worm (*C. elegans*), sea squirt (*C. intestinalis*), fly (*D. melanogaster*), mosquito (*A. gambiae*), zebrafish (*D. rerio*), tetraodon pufferfish (*T. nigroviridis*), Japanese pufferfish (*T. rubripes*), frog (*X. tropicalis*), chicken (*G. gallus*), dog (*C. familiaris*), cow (*B. taurus*), mouse (*M. musculus*), rat (*R. norvegicus*), chimpanzee (*P. troglodytes*), and human (*H. sapiens*). **(B)** The number of tyrosine kinase domains in metazoans and yeast correlates negatively and significantly with the number of distinct cell types. **(C)** The fraction of tyrosines in human-yeast ortholog protein pairs. Every point in the scatter plot represents a human-yeast ortholog protein pair where the (x, y) values denote the tyrosine content in human and yeast proteins, respectively. For simplicity, only proteins with an inferred one-to-one orthologous relationship between human and yeast are analyzed (for example, to avoid accelerated sequence divergence due to functional redundancy of paralogs). Orthologous protein pairs lying above the red diagonal ($x = y$) lines have higher tyrosine com-



position in yeast than in human. The left scatter plot is for 437 human proteins conserved in yeast and known to be tyrosine phosphorylated, and the right plot is for 647 human proteins conserved in yeast not known to be tyrosine phosphorylated.

[127 (7)] and lower genomically encoded tyrosine content (2.3%).

Other factors, such as tyrosine sulfation, could have contributed to the observed tyrosine loss, which raises the question of whether other post-translational modifications and regulatory mechanisms are under similar evolutionary selection that could also explain genomic GC conversion. We observed a strong negative correlation of number of cell types with amino acids that can be methylated or glycosylated (table S1). The numbers of genomically encoded threonine showed strong negative correlations with serine/threonine kinase and cell-type numbers, although these trends were not observed with serine (fig. S2), which suggests possible coarse-grained functional differences between serine- and threonine phosphorylation in metazoans.

Our findings suggest that the implementation of tyrosine kinase signaling, as a biological innovation that probably assisted in the development of multicellular organisms, required system-level adaptive mutations. Analogous to the arguments of John Nash in his dissertation (18), this phenomenon highlights a general principle of adaptive evolution pertaining to the introduction of new

components into a complex system and parallels the evolution of some human societies in which the local populations have to adjust and adapt to the influx of immigrants contributing to the societies' economic development. This principle may serve as an important framework when considering the evolution and fidelity of complex biological systems. Finally, this work raises the possibility that complex regulatory diseases, such as cancer, might result from systems-wide adaptive changes in human genomes and signaling systems.

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Materials and Methods

Figs. S1 and S2

Table S1

References and Notes

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Evolution of a Novel Phenolic Pathway for Pollen Development

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Metabolic plasticity, which largely relies on the creation of new genes, is an essential feature of plant adaptation and speciation and has led to the evolution of large gene families. A typical example is provided by the diversification of the cytochrome P450 enzymes in plants. We describe here a retroposition, neofunctionalization, and duplication sequence that, via selective and local amino acid replacement, led to the evolution of a novel phenolic pathway in Brassicaceae. This pathway involves a cascade of six successive hydroxylations by two partially redundant cytochromes P450, leading to the formation of *N*¹,*N*⁵-di(hydroxyferuloyl)-*N*¹⁰-sinapoylspermidine, a major pollen constituent and so-far-overlooked player in phenylpropanoid metabolism. This example shows how positive Darwinian selection can favor structured clusters of nonsynonymous substitutions that are needed for the transition of enzymes to new functions.

Plant adaptation relies on a remarkable metabolic plasticity that is reflected by the evolution of large gene families. New family members may emerge by segment duplication (sometimes followed by exon shuffling), gene fusion, or retroposition; that is, reverse transcription of mRNAs followed by insertion of the intronless cDNA into the parent genome (1). A striking example of duplication for gene cluster evolution in the triterpenoid metabolism was recently described (2). A survey of the *Arabidopsis* and rice genomes identified several retroposons (3, 4), but retrogene evolution for the acquisition of novel functions was well described only in mammals or insects (1).

We recently performed a global coexpression analysis to predict the function of orphan cytochrome P450 genes in *Arabidopsis thaliana* (5). A candidate emerged with a predicted function in a new branch of phenolic metabolism. *CYP98A8* (AT1G74540) and its paralog *CYP98A9* (AT1G74550) are two chromosome 1–clustered duplications of an ancestor of *CYP98A3*, the latter previously shown to *meta*-hydroxylate the *p*-coumaric esters of shikimic/quinic acids to form lignin monomers (6, 7). *CYP98A8* and *CYP98A9* share only about 50% protein identity with *CYP98A3*, but they do belong to the monophyletic *CYP98A* clade that includes all confirmed 4-coumaroyl shikimate/quinic meta-

hydroxylases; but in protein phylogenies, *CYP98A8* and *CYP98A9* appear separated from vascular plant sequences by *CYP98s* from conifers and moss (fig. S1B). This means either that *CYP98A8* and *CYP98A9* diverged before angiosperm evolution or that they appeared recently and evolved fast, and were thus placed at the base of the clade because of long-branch attraction. In favor of the latter hypothesis, cDNA phylogenies show that *CYP98A8* and *CYP98A9* form a sister group with *CYP98A3* (Fig. 1A and fig. S1D), and no potential orthologs of *CYP98A8* exist in the TIGR Plant Transcript Assemblies and PlantGDB databases, except for a single transcript assembly (*CYP98A53*) from *Brassica napus*. *CYP98A8* and *CYP98A9* are intronless, whereas all other known higher plant *CYP98As* contain two introns at conserved positions, including one that is considered a signature of the expanded *CYP71* clan to which the *CYP98* family belongs (8). This indicates a gene birth event via mRNA-mediated transposition.

Ratios of nonsynonymous and synonymous substitution rates (*dN/dS* or ω) were first es-

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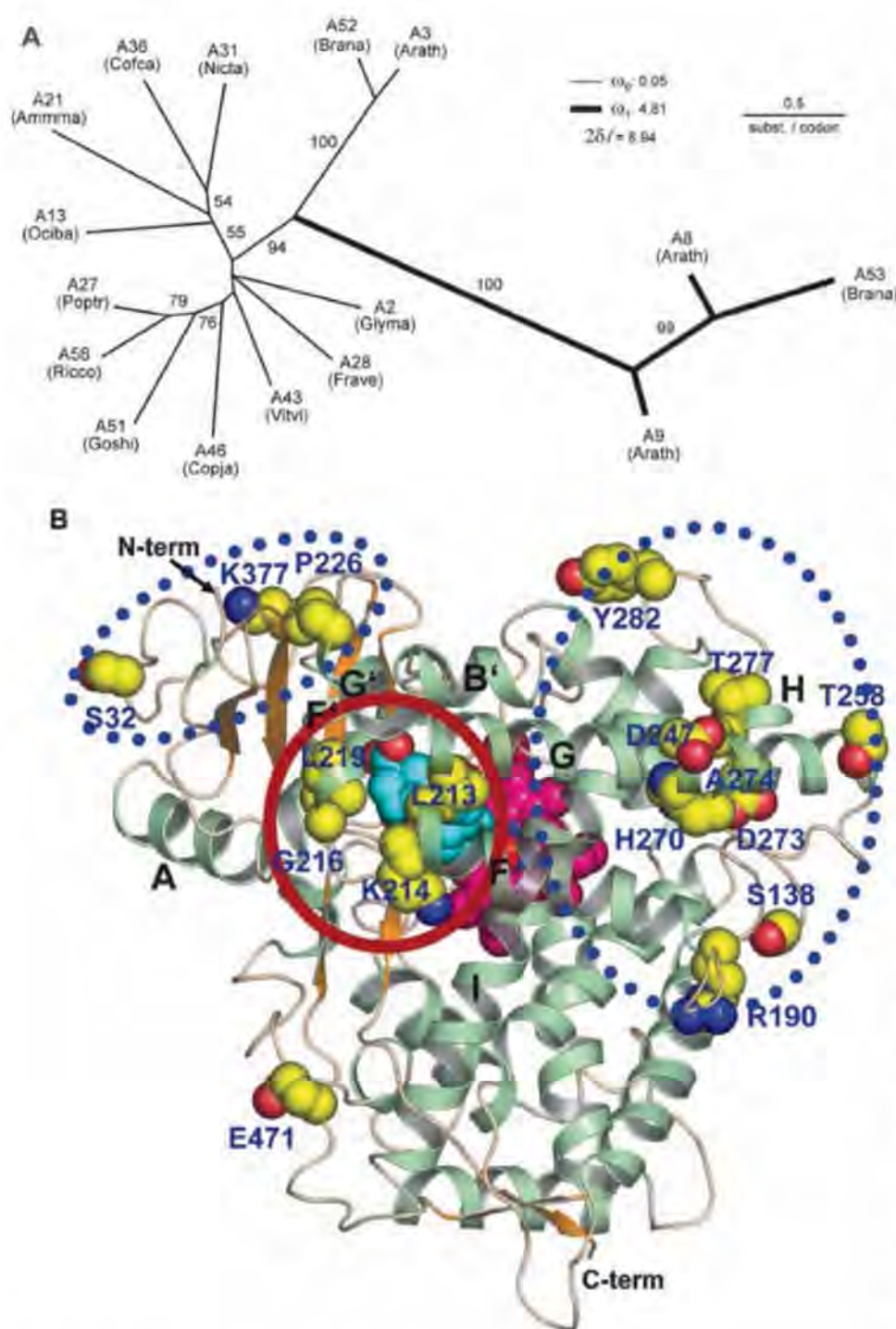


Fig. 1. (A) DNA phylogeny and codon substitution analysis based on near-full-length open reading frames (alignment shown in fig. S1C). Maximum parsimony and maximum likelihood analyses were performed using the Phylip package. Shown is the most parsimonious tree topology (input tree used for further analyses) with bootstrap values (100 replicates). After selection of background and foreground sequences (*CYP98A8*, *CYP98A9*, and *CYP98A53*), the branch site model A implemented in codeml of the paml (v.4) package was used to estimate substitution rates (ω or dN/dS) per codon in the background (ω_0) and the foreground (ω_1) lineages. Branch lengths are drawn to scale (substitutions per codon) as indicated. For details, see (11). Replicate analysis using a maximum likelihood phylogeny is shown in fig. S1D. (B) Overall view of *CYP98A3*/p-coumaroylshikimate complex homology model (32). Residues under positive selection in *CYP98A8* and *CYP98A9* are labeled in dark blue and represented as spheres (carbon, yellow; oxygen, red; nitrogen, blue) at the equivalent locations in *CYP98A3*. Also shown as spheres are heme (carbon, pink) and p-coumaroylshikimate (carbon, cyan). Red solid circle, active site residues; blue dotted ellipses, surface residues. For a close-up view of the active site, see fig. S4.

timated for each branch across the complete sequences with the use of the free-ratio model (9). This already indicated high ω values in the branches leading to *CYP98A8*, *CYP98A9*, and *CYP98A53*, but it was primarily used to identify appropriate background sequences that are clearly under purifying selection ($\omega < 0.1$) across the complete coding region. We expected only a fraction of the coding sequence (the substrate-binding site) to be under positive selection. Thus, the selected background sequences (under purifying selection) were compared with the foreground composed of *CYP98A8*, *CYP98A9*, and *CYP98A53* by using the branch-site model of positive selection, which tests for positive selection at only a few sites along a few lineages (10, 11). Whereas the ω estimate for the background was close to zero ($\omega_0 = 0.05$), a ratio far above 1 was found for the foreground ($\omega_1 = 4.81$, Fig. 1A). To ensure positive selection, this model was compared to a null hypothesis assuming neutral evolution in the foreground (that is, ω_1 was fixed to 1). Based on a likelihood ratio test ($2\Delta l = 8.94$), the hypothesis assuming positive selection in the foreground *CYP98A8*, *CYP98A9*, and *CYP98A53* clade (Fig. 1A) was accepted ($P < 0.01$) with a critical value at the 1% levels of 5.99 (12). The most likely scenario is thus that *CYP98A8* and *CYP98A9* evolved recently at an accelerated rate and under positive Darwinian selection.

Seventeen amino acid residues show a high posterior probability of positive selection (based on the Bayes Empirical Bayes method) (fig. S2). Homology modeling based on the CYP2C8 crystal structure (13) was used to predict the resulting differences between *CYP98A3*, *CYP98A8*, and *CYP98A9* (Fig. 1B and figs. S3 and S4). Residues under positive selection are spatially clustered into three groups (Fig. 1B). One of these groups includes four residues that are located on the roof of the active site, at the end of helix F and in helix F', forming the cavity distal from the heme that interacts with the conjugate moiety of the substrate. Moreover, three residues are missing from helix B' in *CYP98A8* and *CYP98A9* as compared with *CYP98A3*. This region was described in CYP2C8 as a potential substrate-access channel (13, 14). In the *CYP98A8* and *CYP98A9* models, this cavity and the substrate-access channel are larger. In contrast, active-site residues interacting with the coumaroyl moiety of the *CYP98A3* substrate in the vicinity of the heme show strong conservation and a low probability of positive selection (fig. S4). The other two groups under positive selection are located on the protein surface. One is spatially near the N terminus and could participate in membrane interaction. The second forms a large cluster in a region that is responsible for active-site opening via translation of helices F and G in other P450s [supporting online material (SOM) text]. Modifications in *CYP98A8* and *CYP98A9* structures are thus highly clustered. They are predicted to enlarge the distal region of the active-site cavity and substrate-access channel as compared with

CYP98A3. They may also suggest a change in enzyme plasticity. Rapid evolution of the *CYP98A8* and *CYP98A9* genes thus appears to result in functional adaptation.

Analysis of in silico transcriptome (Fig. 2A) (5) and of *promoter::β-glucuronidase (GUS)* transformed plants (Fig. 2B to 2O) (11) indicates a shift from predominant expression in the vasculature of roots, stems, and flowers for *CYP98A3* to a very strong expression in inflorescence tips, young flower buds, and stamen (especially tapetum and pollen) for both *CYP98A8* and *CYP98A9*, and root tip for *CYP98A9*. Expression in aging vasculature was, however, also detected for *CYP98A9*. The evolution of *CYP98A8* and *CYP98A9* thus seems related to the recruitment of a resident promoter (SOM text and fig. S5A) resulting from retroposition that favored the acquisition of a new function in anther and pollen development.

CYP98A8 and *CYP98A9* catalytic function was investigated by ultraperformance liquid chromatography–mass spectrometry (UPLC-MS/MS). A major metabolite that is present in wild-type flower buds, N^1,N^5 -di(hydroxyferuloyl)- N^{10} -sinapoylspermidine (735 daltons) (15–17), was replaced by lower amounts of a more hydrophilic compound, N^1,N^5,N^{10} -triferuloylspermidine (673 daltons), in homozygous *cyp98A8* insertion mutants (SALK_131366; Fig. 3; figs. S5B, S6, and S7; and table S1). Conversely, a significant increase of the 735-dalton compound was observed in the buds of wild-type plants transformed with a *CaMV35S::CYP98A8* construct (Fig. 3). We thus concluded that *CYP98A8* catalyzes the meta-hydroxylation of the three triferuloylspermidine phenolic rings, which is analogous to CYP84 function in the phenylpropanoid metabolism (18).

N^1,N^5,N^{10} -triferuloylspermidine [obtained by chemical synthesis (11)] was then incubated with the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and *CYP98A8* in recombinant yeast microsomes (11). This gave rise to mono-, di-, and a trace of tri-hydroxylated products (fig. S7), thus confirming triferuloylspermidine meta-hydroxylase activity.

CYP98A9-silenced mutants were generated by RNA interference (RNAi), because no insertion mutant was available (11). A line with 70% suppression of *CYP98A9*, but no modification in *CYP98A8* expression (table S1), was selected for UPLC-MS/MS profiling. Significant reduction in N^1,N^5 -di(hydroxyferuloyl)- N^{10} -sinapoylspermidine in flower buds was concomitant with the appearance of N^1 -hydroxyferuloyl- N^5 -caffeoyl- N^{10} -sinapoylspermidine (705 daltons; Fig. 3 and fig. S6). The contribution of *CYP98A9* to phenolamide synthesis was confirmed by a strong increase of the 735-dalton compound in the wild-type plants transformed with a *CaMV35S::CYP98A9* construct (Fig. 3). No hydroxylation of triferuloylspermidine was, however, observed with recombinant *CYP98A9* (fig. S7).

A homozygous *cyp98A8* mutant was crossed with homozygous *cyp98A9* RNAi-silenced plants. Profiling of the buds from F_2 homozygous

cyp98A8 mutants in which *CYP98A9* was confirmed to be silenced (table S1) showed a minor residual peak of N^1,N^5,N^{10} -triferuloylspermidine and the accumulation of significant amounts of N^1 -feruloyl- N^5,N^{10} -dicoumaroylspermidine and N^1 -coumaroyl- N^5,N^{10} -diferuloylspermidine (Fig. 3). The latter were also detected in low quantities in *cyp98A8* plants. Reduced levels of triferuloylspermidine were, on the other hand, detected in *cyp98A8* as compared to the N^1,N^5 -di(hydroxyferuloyl)- N^{10} -sinapoylspermidine found in the wild type. This suggested that both *CYP98A8* and *CYP98A9* contribute to triferuloylspermidine formation. Re-

combinant *CYP98A8* and *CYP98A9* were therefore incubated with N^1,N^5,N^{10} -tri(4-coumaroyl)spermidine (11). Both enzymes led to NADPH-dependent and sequential hydroxylation into mono-, di-, and tri-caffeoylspermidine (fig. S7). *CYP98A8* and *CYP98A9* can thus act redundantly as tricoumaroylspermidine meta-hydroxylases. Accumulation of mono- and di-feruloyl intermediates in the null *cyp98A8* and null *cyp98A8/CYP98A9* RNAi double mutants (Fig. 3 and fig. S6) indicates that the substrate can be released from *CYP98A9* between each hydroxylation step, resulting in product methylation. It also suggests that the

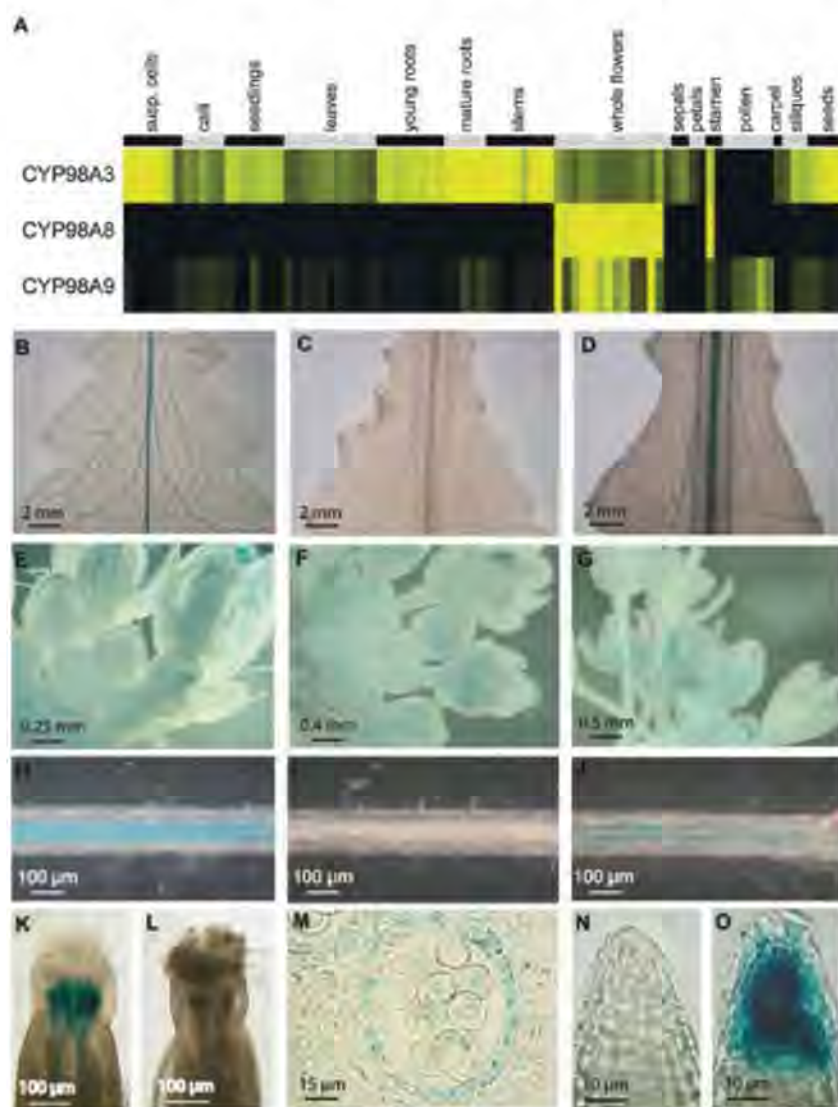


Fig. 2. (A) Selected expression data were retrieved from the Genevestigator database and processed as described in (7). Experiments highlighting the range of organ and tissue expression are shown as a log₂ transformed heat map, with bright yellow indicating greater than 32-fold expression above background (see table S2 for details). susp., suspension. (B to O) Histochemical localization of *GUS* gene expression under the control of *CYP98A3* [(B), (E), (H), (K), and (N)], *CYP98A8* [(C), (F), (I), and (M)], or *CYP98A9* promoters [(D), (G), (J), (L), and (O)]. (B) to (D) In rosette leaves, expression was observed in the vascular system for *CYP98A3::GUS* and in main veins only for *CYP98A9::GUS* (magnification $\times 4$). (E) to (G) Both *CYP98A8::GUS* and *CYP98A9::GUS* were expressed in developing anthers, whereas *CYP98A3::GUS* expression was detected in the petal vascular system ($\times 15$). (H) to (J) In roots, GUS expression was observed in vascular tissue (stronger for *CYP98A3*), except for *CYP98A8::GUS* lines ($\times 82$). (K) and (L) Details of expression in pistils. Expression is strong in the transmitting tissue of *CYP98A3::GUS* only ($\times 22$). (M) Anther thin sections revealed strong expression in the tapetum in *CYP98A8::GUS* plants ($\times 800$) and *CYP98A9::GUS* (not shown in the figure). (N) and (O). In the root tip, a strong signal was detected in *CYP98A9::GUS* transgenic lines only ($\times 1000$).

methyated intermediates can be processed further only by CYP98A8.

CYP98A3 was previously reported to catalyze the *meta*-hydroxylation of *p*-coumaroyltyramine with low efficiency (19), so its activity on CYP98A8 and CYP98A9 substrates was tested (fig. S7). As compared with its preferred sub-

strate, *p*-coumaroylshikimate, CYP98A3 had no activity on tri(feruloyl)spermidine but had weak activity on tri(*p*-coumaroyl)spermidine. Both CYP98A8 and CYP98A9 have completely lost shikimate/quinate ester hydroxylase activities (6). This confirms that CYP98A8 and CYP98A9 activities result from adaptive evolution.

On the basis of coexpression, CYP98A8 was recently suggested to act in concert with AT2G19070 and AT1G67990 to form an overlooked phenolic pathway (5). Our findings validate this prediction, because both the spermidine hydroxycinnamoyl transferase (SHT) and the *O*-methyltransferases AtTSM1 have recently been shown to be involved

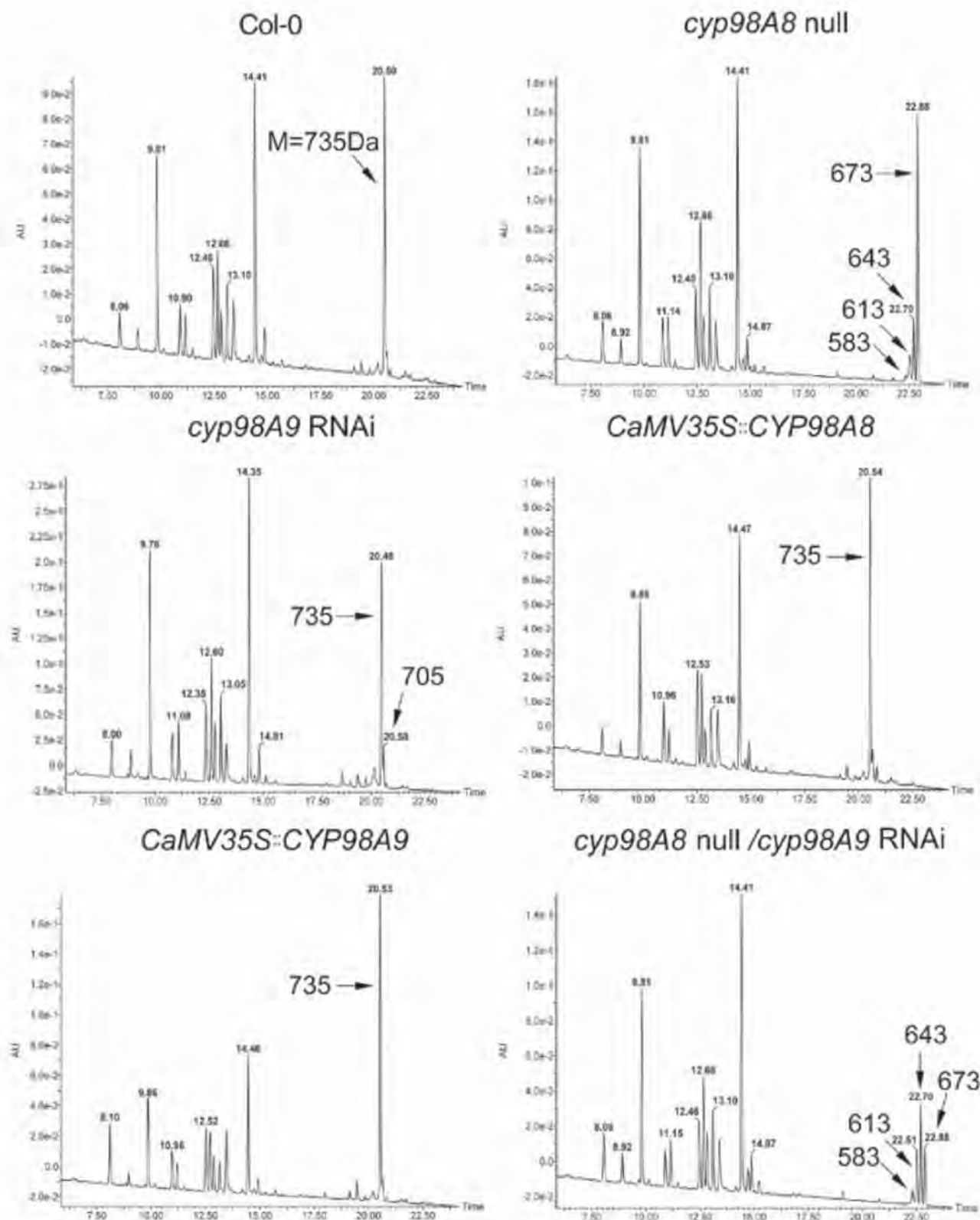


Fig. 3. UPLC-MS/MS analysis of methanol extracts of young inflorescences of wild-type and mutant plants. Shown is UV absorbance at 320 nm. For compound fragmentation and UV spectra, see fig. S6. The peaks eluting between 10 and 15 min are flavonoids.

in the formation of N^1, N^5 -di(hydroxyferuloyl)- N^{10} -sinapoylspermidine (16, 17). This novel pathway (Fig. 4) provides a putative new source of guaiacyl and syringyl precursors, from p -coumaroyl co-enzyme A (CoA), that are available for the formation of biopolymers and phenolic esters. Polyamine oxidation products may, in addition, contribute to the maturation of cell walls (20). Such an alternative route could explain ectopic lignification and conflicting guaiacyl and syringyl end products that accumulate in various mutants of the classical pathway (21, 22). This phenolamide route is independent of the shikimate pool but is more likely to be influenced by nitrogen supply.

Recent evolution argues for the presence of the phenolamide pathway only in Brassicaceae, where hydroxyferuloylspermidines are major pollenit constituents, associated with sporopollenin (16, 17). However, phenolamides are antioxidants, ultraviolet (UV) screens, and antimicrobial compounds (23, 24) that have been found in pollen and inflorescences of most flowering plants

and are associated with fertility and fruit development (25–27). A pathway leading to pollen phenolamides thus exists in other families, but was replaced in the lineage leading to the Brassicaceae. Hydroxylation of p -coumaroylspermidine observed with CYP98A3 raises the possibility that other members of the family evolved the same way. Recent characterization of two acyltransferases of the so-called BAHF family that respectively catalyze the formation of di(sinapoyl) and di(coumaroyl)spermidine in *Arabidopsis* seeds and roots (28) can also be indicative of an original route involving the transfer of readily hydroxylated phenolics to polyamines. The emergence of a novel pathway in Brassicaceae is possibly related to their specific pollen coat composition and formation (29).

CYP98A8 and CYP98A9 provide an example of adaptive gene evolution via retroposition, positive Darwinian selection, and subsequent duplication that led to novel enzymes and plant metabolic pathways (fig. S8). Both genes acquired predominant expression in the anthers

and, via positive selection, evolved a novel function in pollen development. Likewise, most of the successful retrogenes in primates are specifically expressed in the testis and have evolved functional roles in spermatogenesis (1). CYP98A8 and CYP98A9 may be a paradigm example of a similar process operating in plants. Genes mediating sexual reproduction are known to evolve faster than others (30, 31). Their adaptive evolution is thought to be essential for population fitness and contribute to the establishment of fertilization barriers leading to speciation.

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33. We thank J. J. Bourguignon, M. Legrand, E. Grienberger, D. Banner, and S. J. Perlman for helpful advice; D. Nelson for naming P450s; and N. Abdulrazzak for his contribution. M.M. and J.E. are grateful for funding of European Marie Curie actions; D.W.-R., M.M., V.C., and J.-E.B. acknowledge support from the Human Frontier Science program; and J.E. acknowledges support from the Natural Sciences and Engineering Council of Canada.

Supporting Online Material

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Materials and Methods

SOM Text

Figs. S1 to S8

Tables S1 and S2

References

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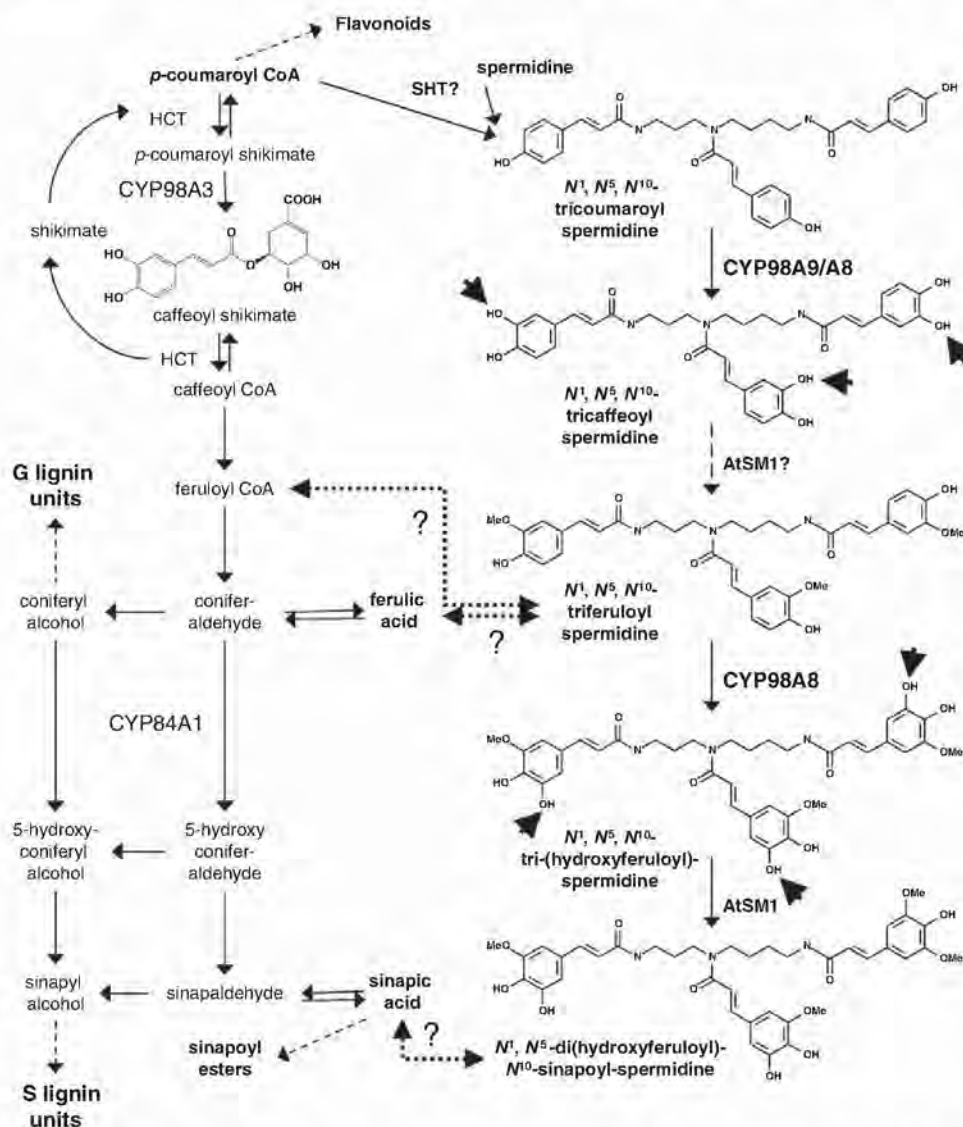


Fig. 4. Proposed catalytic sequence in the novel phenolamide pathway. The formation of the final metabolite without the release of intermediates requires the presence of both CYP98A8 and CYP98A9. HCT, hydroxycinnamoyl transferase; SHT, spermidine hydroxycinnamoyl transferase.

Creating Bacterial Strains from Genomes That Have Been Cloned and Engineered in Yeast

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We recently reported the chemical synthesis, assembly, and cloning of a bacterial genome in yeast. To produce a synthetic cell, the genome must be transferred from yeast to a receptive cytoplasm. Here we describe methods to accomplish this. We cloned a *Mycoplasma mycoides* genome as a yeast centromeric plasmid and then transplanted it into *Mycoplasma capricolum* to produce a viable *M. mycoides* cell. While in yeast, the genome was altered by using yeast genetic systems and then transplanted to produce a new strain of *M. mycoides*. These methods allow the construction of strains that could not be produced with genetic tools available for this bacterium.

We have described the transplantation of the genome of *Mycoplasma mycoides* subspecies *capri* (1–3) from its native cellular environment into a related species, *Mycoplasma capricolum* subspecies *capricolum* (4). We have also described the complete chemical synthesis of the 580-kb *Mycoplasma genitalium* genome (5, 6). Initial stages of the synthesis were carried out by in vitro assembly reactions, and pieces up to a quarter of a genome in size were cloned in *Escherichia coli*. We overcame difficulties in cloning larger segments of DNA in

E. coli by using homologous recombination in the yeast *Saccharomyces cerevisiae* to assemble the subgenomic synthetic DNA segments into a complete *M. genitalium* genome. To complete our construction of a living microbe, we must isolate our synthetic genome from yeast and transfer it into a cellular environment that will accept and execute the genetic instructions sufficient to produce a replicating organism. In this paper, we describe methods for transplanting natural 1.1-Mb *M. mycoides* genomes cloned in yeast into *M. capricolum* recipient cells. These species are more convenient experimental organisms than *M. genitalium* because of their faster growth rate.

M. mycoides was transformed (7) with a vector containing a selectable tetracycline-resistance marker and a β -galactosidase gene for screening. The vector also contained a yeast auxotrophic marker, a yeast centromere, and a yeast auton-

omously replicating sequence, for selection and propagation in yeast as a yeast centromeric plasmid (YCp). Direct genomic sequencing (8) of one clone (YCpMmyc1.1) showed that the entire vector integrated into the genome. This clone grew robustly and transplanted efficiently into *M. capricolum* (9), so it was chosen for cloning into yeast. The genome of this clone will be called YCpMmyc1.1 throughout this paper, regardless of the cellular source. YCpMmyc1.1 can refer to: (i) the original *M. mycoides* strain (the “native” *M. mycoides* YCpMmyc1.1 genome), (ii) the same genome cloned in yeast, (iii) the genome transplanted from *M. mycoides* or from yeast, or (iv) this genome as free DNA from any of these sources.

YCpMmyc1.1 genomes were isolated from *M. mycoides* (9) and transformed into yeast spheroplasts (10) of strains VL6-48N (11) and W303a. Clones were analyzed for completeness and size by multiplex polymerase chain reaction (PCR) and clamped homogenous electric fields (CHEF) gel electrophoresis. To test whether deletions occur during routine propagation in yeast, we screened 40 individual colonies derived from a single intact clone of YCpMmyc1.1 in W303a. All appeared to contain complete genomes (fig. S1), which indicates that this bacterial genome is stable in yeast. Sequences between the amplicons were not interrogated in this experiment; however, sizable deletions would have been detected by this approach, and none were observed. Sequencing of a complete genome transplanted from yeast (see below) provided a definitive demonstration of stability of the *M. mycoides* genome in yeast.

We engineered YCpMmyc1.1 in yeast by creating a seamless deletion in a nonessential Type III restriction endonuclease gene (Fig. 1). This modification cannot be made with the genetic tools available for this bacterium. We first transformed a YCpMmyc1.1 yeast clone with a cassette con-

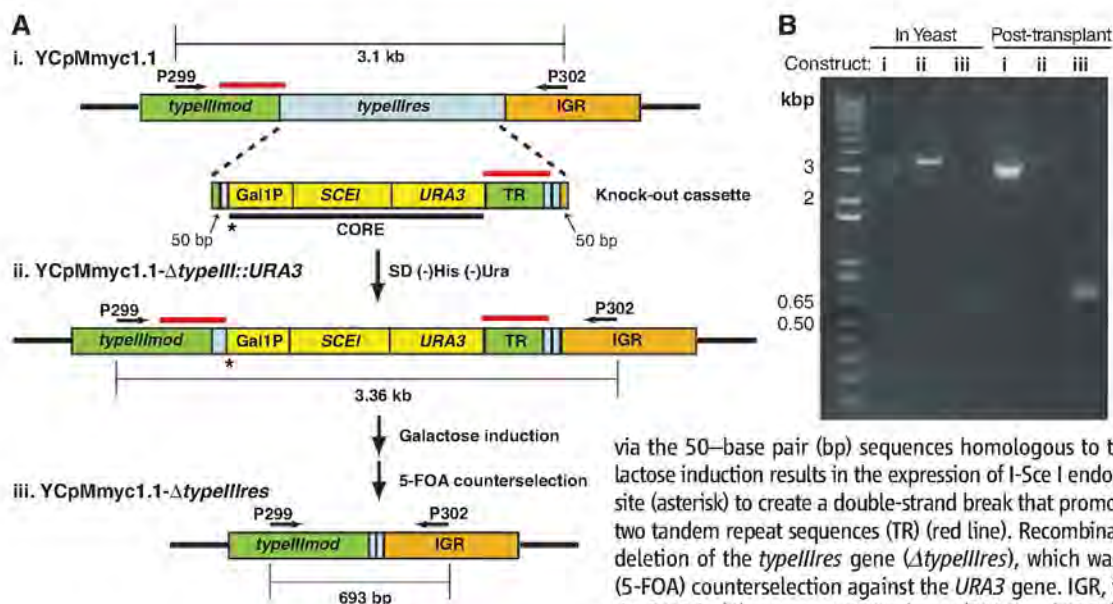


Fig. 1. Generation of Type III restriction enzyme deletions. (A) To make an *M. mycoides* Type III restriction enzyme gene (*typellres*) deletion in yeast (iii), we constructed a linear DNA fragment, knockout cassette, by fusing two PCR products, CORE and tandem repeat sequence (TR) (i). This cassette was then transformed into a yeast W303a strain harboring the YCpMmyc1.1 *M. mycoides* genome (ii). Growth on (-)His (-)Ura medium selected for replacement of the Type III restriction enzyme open reading frame (ORF) by the cassette

via the 50-base pair (bp) sequences homologous to the target sites (Δ typellres::URA3). Galactose induction results in the expression of I-Sce I endonuclease, which cleaves the 18-bp I-Sce I site (asterisk) to create a double-strand break that promotes homologous recombination between two tandem repeat sequences (TR) (red line). Recombination between the TRs creates a seamless deletion of the *typellres* gene (Δ typellres), which was isolated following 5-fluoroorotic acid (5-FOA) counterselection against the *URA3* gene. IGR, intergenic region. (B) The arrows above the DNA in (A) represent PCR primers (P299 and P302) used to verify the presence or absence of the knockout cassette. PCRs of representative transplant clones with (ii) and without (iii) the knockout cassette are shown. PCRs of the YCpMmyc1.1 clone in yeast (i) are shown for comparison. The expected sizes are obtained for each amplicon.

taining a *URA3* marker and the *SCEI* endonuclease gene under the control of the *GAL1* promoter. We selected for insertion of the cassette into the Type III gene. Four of five clones contained intact genomes, and one contained a genome with a large deletion (YCpMmyc1.1-Δ500kb) (figs. S2 and S3). The *URA3* cassette was removed by cleavage at an I-Sce I recognition site near one end of the cassette (Fig. 1). Counter selection with 5-fluoroorotic acid (12) produced clones that had lost the *URA3* cassette. Thus, we obtained two *M. mycoides* YCp genomes, one that contained the *URA3* cassette and the other that contained a seamless deletion of the Type III restriction enzyme gene (Fig. 1A). The changes to the genome were verified by PCR (Fig. 1B).

We isolated YCpMmyc1.1 from yeast and attempted transplantation into wild-type *M. capricolum* cells. However, we did not recover any transplants (Table 1). We reasoned that the principal obstacle was a restriction endonuclease in the recipient *M. capricolum* that degraded the unmethylated YCpMmyc1.1 donor DNA isolated from yeast (fig. S4).

Two methods were used to overcome the *M. capricolum* restriction barrier. First, we inactivated the single restriction enzyme in *M. capricolum* by integration of a puromycin-resistance marker into the coding region of the gene. No detectable restriction enzyme activity was seen in extracts of this altered strain [*M. capricolum* RE(-)] (fig. S5). Removal of *M. capricolum* restriction activity should allow donor *M. mycoides* YCp genomes isolated from yeast to survive initial contact with the *M. capricolum* cytoplasm. The second method was to protect the donor DNA isolated from yeast by *in vitro* methylation, using *M. capricolum* extracts. An extract of *M. mycoides* also protected the incoming donor DNA, because *M. mycoides* contains an ortholog of the system found in *M. capricolum* (fig. S6). The additional restriction-modification systems present in the *M. mycoides* donor genome did not affect transplantation.

We isolated YCpMmyc1.1 from *M. mycoides* and transplanted it into wild-type *M. capricolum* and *M. capricolum* RE(-) recipient cells (fig. S7). Results were scored by selecting for growth of blue colonies on SP4 medium containing tetracycline at 37°C. Successful transplantations were obtained using YCpMmyc1.1 from yeast with both recipient cells (Table 1). Colonies were obtained using *M. capricolum* RE(-) as recipient cells when the donor genomic DNA was untreated, mock-methylated, treated with *M. capricolum* or *M. mycoides* extracts, or treated with purified *M. mycoides* methyltransferases. However, transplantation using wild-type *M. capricolum* recipient cells occurred only when the donor YCp genome from yeast was methylated with *M. capricolum* extract, *M. mycoides* extract, or purified *M. mycoides* methyltransferases. No colonies were obtained when mock-treated or untreated YCpMmyc1.1 was transplanted into wild-type *M. capricolum* recipient cells. Thus, avoidance of

the *M. capricolum* recipient restriction system is vital for successful transplantation of *M. mycoides* YCp genomes from yeast.

YCpMmyc1.1, as well as the engineered YCp genomes (YCpMmyc1.1-Δ*typellres*::*URA3* and YCpMmyc1.1-Δ*typellres*), were also isolated from yeast strain W303a. Transplantation of all three YCp genomes into *M. capricolum* recipient cells resulted in similar numbers of tetracycline-resistant blue colonies (Table 1). The large deletion clone (YCpMmyc1.1-Δ500kb) discussed above served as an appropriate control because it lacks many presumed essential genes yet retains the YCp element and *tetM*. As expected, no colonies were recovered when this genome was transplanted into *M. capricolum* recipient cells.

Recovery of colonies in all these transplantation experiments was dependent on the presence of both *M. capricolum* recipient cells and an *M. mycoides* genome. The experiments described here used donor YCp genome DNA that included yeast genomic DNA. However, purifying the donor YCp genome DNA away from yeast genomic DNA did not substantially alter transplantation results, which suggests that the recipient *M. capricolum* cells are able to tolerate the presence of nonspecific or carrier DNA (Table 1). Positive transplantation results were obtained with donor YCp genome DNA isolated from four independent transformant cultures of strain VL6-48N and four of strain W303a. Thus, bacterial genomes can be stably cloned in both yeast strains.

We verified that the recovered colonies were *M. mycoides* by Southern blot analysis using an *M. mycoides*-specific IS1296 element as probe (Fig. 2A). We showed that the Type III restriction gene was deleted in the engineered bacterium by PCR (Fig. 1B), by Southern blot analysis using the Type III restriction gene sequence as probe (Fig. 2B), and by sequencing the locus (Fig. 2C).

To confirm that our transplants were entirely *M. mycoides* and not chimeras containing yeast sequences or *M. capricolum* recipient cell sequences, we sequenced the genome of one transplant from which the Type III restriction gene had been deleted (GenBank accession no. CP001668) (9). All of the assembled genome matched *M. mycoides*, except for those regions that matched the YCp vector. In addition, except for alterations we made in the genome, our transplant YCpMmyc1.1-Δ*typellres* genome sequence was identical to *M. mycoides* YCpMmyc1.1, which was used to generate the original *M. mycoides* yeast clone. Thus, there was no recombination of either yeast or recipient cell genomes with the *M. mycoides* YCp donor genome, and these bacterial genome sequences are stable as YCps.

Here we describe methods to transfer a genome between branches of life, from a bacterium to a eukaryote, where it can be genetically altered, and then back again into a bacterium (Fig. 3). Our method of yeast vector insertion uses bacterial selection to ensure a viable integration point. This avoids a potentially lethal genome disruption, which would prevent transplantation.

Table 1. Transplantation of *M. mycoides* YCp genomes from yeast into wild-type and RE(-) *M. capricolum* recipient cells. The number of tetracycline-resistant, blue colonies obtained after the transplantation of *M. mycoides* YCp genomes from yeast into *M. capricolum* recipients was counted. Wild-type *M. capricolum* and *M. capricolum* RE(-) transplantation was performed using methods described in fig. S1. For untreated samples, yeast plugs were digested with β-agarase (melting step) and transplanted into both recipient cells. The treated samples were methylated and treated with proteinase K before the melting step. The mock-methylated sample was treated the same as the methylated samples, except that no extract or purified methyltransferases were added. VL6-48N yeast agarose plugs used in this experiment carried YCpMmyc1.1. W303a yeast agarose plugs carried YCpMmyc1.1, YCpMmyc1.1 that was engineered in yeast (YCpMmyc1.1-Δ*typellres*::*URA3* or YCpMmyc1.1-Δ*typellres*), or YCpMmyc1.1-Δ500kb. The number of transplants is the average of at least three experiments. The error reported is the absolute mean deviation.

Yeast strain	Genome	Methylation treatment	Number of transplants (colonies or plugs)	
			<i>M. capricolum</i> RE(-)	Wild-type <i>M. capricolum</i>
VL6-48N	YCpMmyc1.1	Untreated	37 ± 3	0
		<i>M. capricolum</i> extracts	32 ± 13	9 ± 4
		<i>M. mycoides</i> extracts	15 ± 8	22 ± 8 [13 ± 4]*
		Mock-methylated	34 ± 17	0
		<i>M. mycoides</i> purified methylases	20 ± 17	13 ± 10
W303a	YCpMmyc1.1	Untreated	22 ± 5	Not done
	YCpMmyc1.1-Δ <i>typellres</i> :: <i>URA3</i>	Untreated	52 ± 10	Not done
	YCpMmyc1.1-Δ <i>typellres</i>	Untreated	52 ± 12	Not done
	YCpMmyc1.1-Δ500kb	Untreated	0	Not done

*Yeast plugs were cleared of yeast genomic DNA by digestion with a cocktail of Asi SI, Rsr II, and Fse I followed by pulsed-field gel electrophoresis. †Yeast plugs were cleared of yeast genomic DNA by using pulsed-field gel electrophoresis.

Full-length clones of mycoplasma genomes have proven stable in yeast during routine propagation and genome transplantation. As described, 40 individual colonies derived from a complete YCp clone of the *M. mycoides* genome all contained full-length genomes. Furthermore, eight indepen-

dent full-length yeast clones of the *M. mycoides* genome yielded viable bacteria when the genome was transplanted. Finally, the complete genome sequence of *M. mycoides* was unchanged during cloning into yeast and transplantation back into a bacterial cell. We have never seen deletions in

our YCp clones except after selection following DNA transformation.

We previously reported transplantation of naked genomic DNA purified from *M. mycoides* cells (4). The transplant events were rare, and there remained the possibility that they resulted from damaged cells that could be somehow repaired in the presence of recipient cells, or from genomes that were in complex with some *M. mycoides* component other than genomic DNA. Transplantation from yeast of the nonmethylated *M. mycoides* genome into the *M. capricolum* RE(-) recipient cells eliminates the possibility that components of the *M. mycoides* cells are required for transplantation (fig. S7).

Our original transplant experiments used genomes that were resistant to the restriction enzyme of the recipient cells because the donor cells contain the same restriction modification system as the recipient cell (4). *M. mycoides* DNA sequences from yeast lack the specific methylations imparted by *M. mycoides* restriction modification systems. The natural DNA sequences encoding the methylases cannot be expressed because they contain UGA tryptophan codons, which function as stop codons in yeast. Transplantation from yeast was achieved either by methylation of the donor genome in vitro or by inactivation of the restriction enzyme in the recipient cell. It was unnecessary to protect the *M. mycoides* genome from its own restriction systems, because either inactivation of the recipient cell's endonuclease or methylation with the recipient cell's methylase was sufficient to allow transplantation. When transplanting other bacterial genomes from yeast, it may be necessary to methylate the donor genome in vitro to protect it from its own restriction enzymes.

Genetic manipulation of *M. mycoides*, and mycoplasmas in general, is limited. Integration of plasmid DNA by single crossover events allows the targeted addition or disruption of genes in *M. mycoides* (13). However, because there are only a few selection markers, the number of genetic alterations that can be performed in a single *M. mycoides* cell is limited. The maintenance of the *M. mycoides* genome in yeast allowed us to access the powerful repertoire of yeast genetic methods and to produce an *M. mycoides* strain that had not previously existed. Thus, we report engineering of a bacterial cell by altering its genome outside of its native cellular environment.

It is now possible to readily generate *M. mycoides* strains with multiple targeted gene deletions, insertions, and rearrangements. It would also be possible to engineer bacterial genomes in yeast by using random mutagenesis methods so that transplantation would yield populations of altered bacteria. After screening for a desired trait, these methods could be reapplied in a cyclical manner to introduce new traits (Fig. 3). This transplantation system potentially allows *M. mycoides* and closely related species to be model systems for exploring the pathogenicity and biology of mycoplasmas. The *mycoides* group of mycoplasmas causes major diseases of ruminants, and there is an urgent

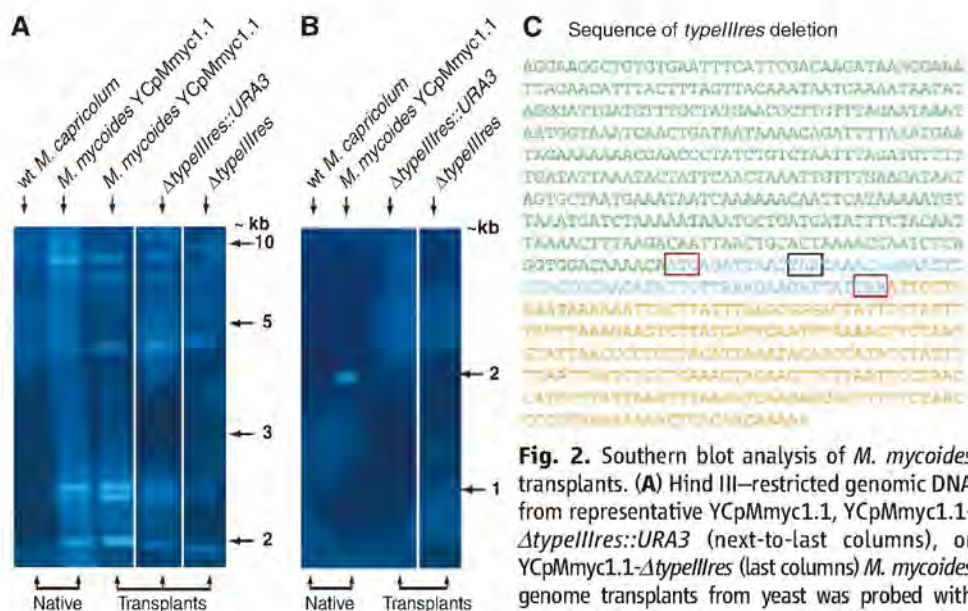
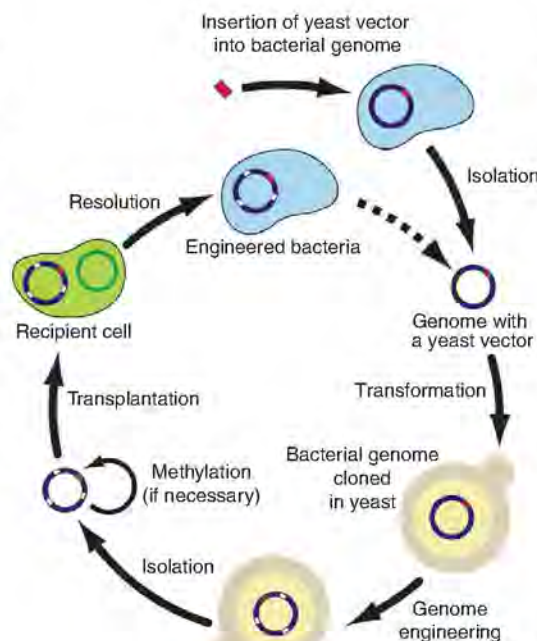


Fig. 2. Southern blot analysis of *M. mycoides* transplants. (A) Hind III–restricted genomic DNA from representative YCpMmyc1.1, YCpMmyc1.1- Δ typellres::URA3 (next-to-last columns), or YCpMmyc1.1- Δ typellres (last columns) *M. mycoides* genome transplants from yeast was probed with IS1296 sequences. The genomic DNAs of native *M. mycoides* YCpMmyc1.1 cells and *M. capricolum* recipient cells were also probed for comparison. All of the selected transplant colonies contain the same IS1296 pattern as native *M. mycoides* YCpMmyc1.1. (B) The engineered *M. mycoides* transplants were tested for the absence of the Type III restriction enzyme gene by Southern blot analysis (representative clones shown). Eco RV–restricted genomic DNA from YCpMmyc1.1- Δ typellres::URA3, and YCpMmyc1.1- Δ typellres *M. mycoides* cells derived by genome transplantation was probed with the *typellres* gene sequence. The genomic DNAs of native *M. mycoides* YCpMmyc1.1 cells and *M. capricolum* recipient cells were also probed for comparison. The *typellres* gene is absent in the engineered genomes but present in the native *M. mycoides* YCpMmyc1.1 genome. (C) Sequencing of the seamless deletion region of the YCpMmyc1.1- Δ typellres *M. mycoides* genome transplant verified that the Type III restriction gene was removed as designed. The sequence text colors are the same as the gene region colors in the genetic maps in Fig. 1. A small portion of the *typellres* gene remained after the deletion because of the overlap between the *typellmod* and *typellres* genes. The start and stop codons of the *typellres* gene are boxed in red; the stop codon of the *typellmod* gene is boxed in black.

Fig. 3. Moving a bacterial genome into yeast, engineering it, and installing it back into a bacterium by genome transplantation. A yeast vector is inserted into a bacterial genome by transformation. That genome is cloned into yeast. After cloning, the repertoire of yeast genetic methods is used to create insertions, deletions, rearrangements, or any combination of modifications in the bacterial genome. This engineered genome is then isolated and transplanted into a recipient cell to generate an engineered bacterium. Before transplantation it may be necessary to methylate the donor DNA in order to protect it from the recipient cell's restriction system(s). This cycle can be repeated starting from the newly engineered genome (dashed arrow).



need for vaccines (14, 15). This technology could accelerate the construction of live vaccine strains.

Many medically or industrially important microbes are difficult to manipulate genetically. This has severely limited our understanding of pathogenesis and our ability to exploit the knowledge of microbial biology on a practical level. We hope that the cycle presented here can be applied to other species, to help solve these problems.

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Supporting Online Material

www.sciencemag.org/content/full/1173759/DC1
Materials and Methods

Figs. S1 to S7

Table S1

References

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On Universality in Human Correspondence Activity

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The identification and modeling of patterns of human activity have important ramifications for applications ranging from predicting disease spread to optimizing resource allocation. Because of its relevance and availability, written correspondence provides a powerful proxy for studying human activity. One school of thought is that human correspondence is driven by responses to received correspondence, a view that requires a distinct response mechanism to explain e-mail and letter correspondence observations. We demonstrate that, like e-mail correspondence, the letter correspondence patterns of 16 writers, performers, politicians, and scientists are well described by the circadian cycle, task repetition, and changing communication needs. We confirm the universality of these mechanisms by rescaling letter and e-mail correspondence statistics to reveal their underlying similarity.

Power law statistics are a hallmark of critical phenomena. A less obvious characteristic of criticality is the emergence of universality classes that capture the similarity of seemingly disparate systems. For example, despite the fact that water and carbon dioxide have different chemical properties, they were observed to behave in the same manner when close to their respective critical points (1). This is because idiosyncrasies, such as the existence of electric dipoles or the ability to form hydrogen bonds, become irrelevant near the liquid/gas critical point. For physical systems, renormalization group theory (2, 3) has enabled researchers to understand the deep connection between the symmetries of a system and the mechanisms that underlie its behavior. The similarity of different fluids near their respective liquid/gas critical points is often demonstrated by rescaling their statistics so that they collapse onto the same universal curves (often power law curves), which have particular scaling exponents. By grouping different substances into the same universality class, as identified by its scaling exponents, one discovers that fluids are described by the same statistical laws near the liquid/gas critical point as uniaxial magnets are near their paramagnetic critical point (1). One can also differentiate the behavior of these systems from the behavior of polymers near the sol/gel transition, which belong to a different universality class (1).

In addition to describing critical phenomena, power law scaling has also been widely reported in biology, economics, and sociology (4–10). Renormalization group theory therefore offers a tantalizing hypothesis for the prevalence of particular power law scaling exponents in social systems: Social systems, in analogy with physical systems, may operate near critical points and can therefore be classified into a small number of distinct universality classes. A heated debate has consequently ensued in the literature concerning the “universal-

ity of human systems” (in the statistical physics meaning of the phrase). Is there enough statistical evidence for the asymptotic power law description of the heavy-tailed distributions reported in human systems (11–14)? Is it reasonable to postulate that social systems, like their physical counterparts (2, 3, 15), can be classified into universality classes according to scaling exponents (16)?

Human correspondence is a paradigmatic area where the matters of power law scaling and universality are contentious issues. One view that has recently received considerable attention in the literature (17, 18) posits that correspondence patterns are driven primarily by the need to respond to other individuals. This is formalized by a priority queueing model (19), which, under certain limiting conditions, reproduces the asymptotic scaling of empirically observed heavy-tailed correspondence statistics. In particular, the heavy-tailed statistical properties of e-mail correspondence are reportedly reproduced by a fixed-length queue with a single task type (19, 20), whereas the heavy-tailed statistical properties of letter correspondence are reportedly reproduced by either a variable-length queue with a single task type (21, 20) or by a fixed-length queue with multiple task types (22). The fact that there are different exponents for the two modes of correspondence has been taken as evidence that human correspondence falls into one of two universality classes (20). When interpreted in the statistical mechanics sense of universality, one would conclude that e-mail and letter correspondence are fundamentally different activities.

In contrast, we hypothesize that human correspondence patterns are not driven by responses to others but by more prosaic mechanisms: the circadian cycle, task repetition, and changing communication needs. We formalize these mechanisms with a cascading, nonhomogeneous Poisson process that we have previously shown to be statistically consistent with e-mail communication patterns (14). We hypothesize that the same model is capable of describing letter correspondence and that the heavy-tailed correspondence statistics primarily arise from the variation in an individual's communication needs over the course of his or her lifetime.

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We obtained the letter correspondence records for 16 writers, performers, politicians, and scientists. Each data set consists of a list of letters that were sent by each of these individuals, and each record comprises the name of the sender, the name of the recipient, and the date when the letter was written [see supporting online material (SOM) text S1 for details]. The nature of the data raises two issues to consider during analysis. First, the precise authorship date of some letters is unknown, so we restricted our analysis to only those letters that have precise authorship dates. Second, it is highly unlikely that all of the letters written by a particular individual are present in the database. We have confirmed that our results are insensitive to sampling effects from this method of data collection (SOM text S2).

An important consideration in studying the letter correspondence patterns of these individuals is that the data cover their entire lifetimes. As a result, it is conceivable that changing communication needs might affect letter correspondence patterns. For example, before Einstein became widely known, the bulk of his recorded communication was to friends and relatives. After the confirmation of his theory of relativity in 1919, Einstein's need to communicate with other individuals substantially increased. By that time, his stepdaughter Ilse Einstein was helping him with secretarial tasks, resulting in greatly improved coverage of his recorded correspondence (23). Because of this secretarial assistance and his increased fame, we expect that the average time between consecu-

tively sent letters, the average interevent time $\langle\tau\rangle$, is significantly larger during the beginning of Einstein's life than during the latter part of his life. Our expectations are verified in Fig. 1, A and B, demonstrating that these time series are nonstationary; that is, the heavy-tailed τ distribution results from a mixture of time scales (24).

Because these time series are nonstationary, we partitioned each complete time series into smaller time segments so that we could approximate stationary behavior within each time segment. We accomplished this by splitting the time series into segments lasting 364 days (52 weeks), unless fewer than 10 events fell within that time period, in which case consecutive segments were merged until this criterion was met.

Assuming that the correspondence patterns within each time segment are stationary, we can then model the behavior within each time segment with standard techniques. As a first approximation, one might naively expect that letters are sent at a constant rate ρ and that the time at which every letter is sent is independent of all others. Such a process is referred to as a homogeneous Poisson process, which gives rise to an exponential τ distribution $p(\tau) = \rho e^{-\rho\tau}$. Whereas the tail of the τ distribution within these time segments is approximately exponential, the best-estimate predictions of a homogeneous Poisson process do not produce the correct decay rate (Fig. 1C). This suggests that only a few changes to the homogeneous Poisson process are needed to reproduce the observed τ distribution. We hypothesize that, as for

e-mail correspondence, two additional ingredients must also be considered for modeling letter correspondence (14).

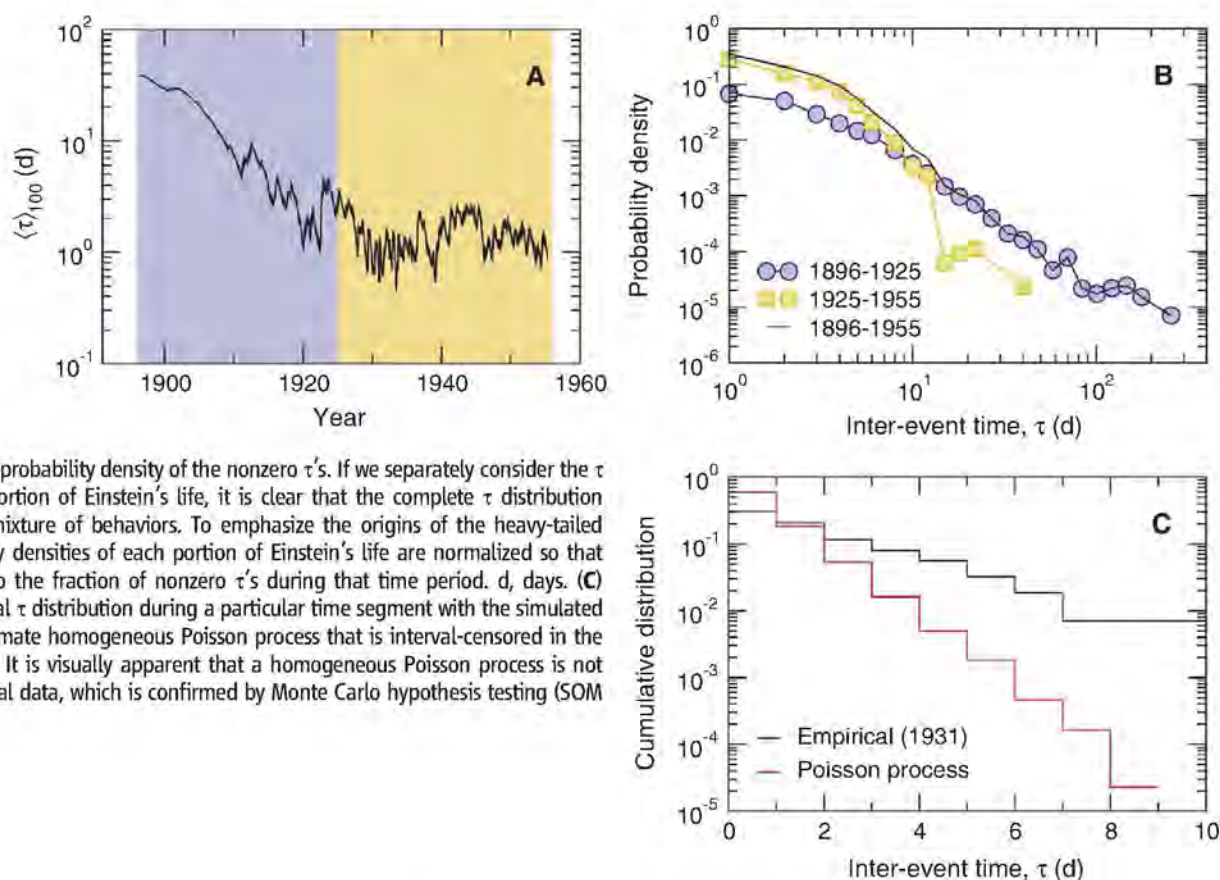
First, circadian and weekly cycles of activity may influence when individuals communicate. Previously, we accounted for these cycles of activity in e-mail communication with a nonhomogeneous Poisson process whose rate $\rho(t)$ changes periodically on daily and weekly time scales. For letter correspondence, however, the resolution of the data does not permit us to identify activity patterns within a day, and day-to-day changes in activity provide no additional insight (SOM text S3). We therefore approximate the nonhomogeneous Poisson process $\rho(t)$ by a homogeneous Poisson process with constant rate ρ_i during time segment i ; that is, we model the rate of activity $\rho(t)$ throughout each individual's life by a piecewise constant function of time.

Second, individuals are much more likely to continue writing letters once they have written one letter, in order to use their time more effectively. We account for this behavior by hypothesizing that, once an individual finishes writing a letter, there is a probability ξ_i that they will write another letter. This process repeats itself until this cascade of additional letters concludes with probability $1 - \xi_i$, at which point the individual's behavior is again governed by a homogeneous Poisson process with rate ρ_i (25). We refer to the resulting model as a cascading Poisson process.

To compare the predictions of the cascading Poisson process (26) to the empirical data, we

Fig. 1. Nonstationarity of Albert Einstein's letter correspondence activity. We selected Einstein as an example, but nonstationarities are present for all 16 writers, performers, politicians, and scientists studied here. (A) Average of τ over 100 consecutive τ 's. During the beginning of Einstein's life (blue-shaded region), $\langle\tau\rangle_{100}$ is significantly larger than during the end of his life (orange-shaded region).

(B) Logarithmically binned probability density of the nonzero τ 's. If we separately consider the τ distribution during each portion of Einstein's life, it is clear that the complete τ distribution (black line) is actually a mixture of behaviors. To emphasize the origins of the heavy-tailed distribution, the probability densities of each portion of Einstein's life are normalized so that their integrals are equal to the fraction of nonzero τ 's during that time period. d, days. (C) Comparison of the empirical τ distribution during a particular time segment with the simulated predictions of the best-estimate homogeneous Poisson process that is interval-censored in the same manner as the data. It is visually apparent that a homogeneous Poisson process is not consistent with the empirical data, which is confirmed by Monte Carlo hypothesis testing (SOM text S3).



must first estimate the parameters $\theta_i = \{\rho_i, \xi_i\}$ from the data during each time segment. The nature of the data, however, raises an important

concern for parameter estimation: Because each event is only known to occur within a particular day, not at a precise time of the day, the data are

interval-censored (27). We account for the interval-censored data and calculate the best-estimate parameters $\hat{\theta}_i$ by numerically maximizing the censored likelihood function (see SOM text S4 for the derivation).

The resulting best-estimate parameters $\hat{\theta}_i$ provide insight into the correspondence patterns of each individual (Fig. 2, A and B, and fig. S4). For example, whereas both Schoenberg and Einstein have a 50-fold increase in the rate at which they send letters, presumably due to their increasing correspondence obligations and a more complete sampling of their overall letter correspondence, their use of cascades of activity is markedly different. Schoenberg, for instance, sent about 21% of his letters during cascades of multiple letters throughout his life. In contrast, Einstein rarely used cascades of activity as a young man (before 1910), whereas in later years (after 1933), he sent approximately 34% of his letters during cascades of multiple letters.

In the period 1928–1933, Einstein sent over 50% of his letters during cascades of multiple letters. The start of this period coincides with the hiring of Einstein's long-time secretary Helen Dukas, who more systematically retained copies of his outgoing correspondence. After the Nazis took power in January 1933, his correspondence patterns change markedly; this possibly reflects changes in his correspondence obligations at the Institute for Advanced Study at Princeton University after immigrating to the United States in late 1933 (23).

Of course, inferring how an individual's behavior changes based on a model's parameter estimates is contingent on the model being consistent with the data. We tested the statistical consistency of our model with the data by Monte Carlo hypothesis testing (SOM text S5). We reject the model during a particular time segment if the P value obtained from the Monte Carlo hypothesis testing procedure is less than a threshold of 0.05. Because this threshold is greater than zero, it means that there is a finite chance that we will reject the hypothesis that the model is consistent with the data even if the data were generated from the model.

If we assume that each time segment is independent, then we would expect to reject each of the time segments with a 5% chance, and the total number of rejections is expected to be distributed according to a binomial model (28). Out of the 54 independent time segments for Einstein, for example, we would expect to reject the model 2.7 times, with 0 to 6 defining the bounds of the 95% confidence interval (CI) of the corresponding binomial model. For Einstein, our procedure rejects the cascading Poisson process for 2 out of 54 time segments, indicating that we cannot reject the hypothesis that the model is able to explain his correspondence patterns. Indeed, our hypothesis testing confirms that the cascading Poisson process cannot be rejected as an explanatory model for the letter correspondence of any of the individuals under consideration (Table 1). These results

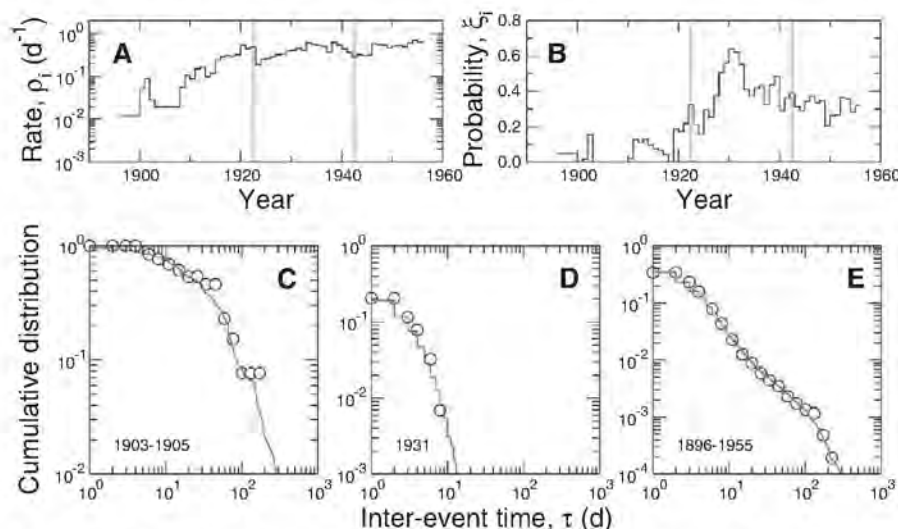


Fig. 2. Origin of heavy-tailed τ distribution for Albert Einstein. We selected Einstein as an example, but the same explanation is relevant for all 16 writers, performers, politicians, and scientists studied here. (A and B) We estimate the parameters $\theta_i = \{\rho_i, \xi_i\}$ by maximizing the censored likelihood function for each time segment (SOM text S4). Gray-shaded regions denote time segments during which the cascading Poisson process was rejected by Monte Carlo hypothesis testing. Parameter estimates for all individuals studied here are shown in fig. S4. There is a 50-fold changes in the rate ρ_i and dramatic changes in ξ_i for Einstein. (C and D) Cumulative distribution of τ 's (circles) for Einstein during 1903–1905 and 1931. The data agree with the predictions of a nonstationary cascading Poisson process (red line) with the best-estimate parameters shown in (A) and (B). The model predictions are generated numerically by running the model defined by $\theta(t)$ 10 times and interval-censoring the resulting synthetic time series in the same manner as the empirical data. (E) The cumulative distribution of τ 's (circles) for Einstein over his entire life. The data agree with the predictions of a nonstationary cascading Poisson process (red line) with the best-estimate parameters shown in (A) and (B). The τ distributions for all 16 letter correspondents studied here are shown in fig. S5. These results clarify the origin of the heavy-tailed τ distribution.

Fig. 3. Collapse of τ distributions for letter and e-mail correspondence. (A) Cumulative distribution of τ 's for all 16 letter correspondents (red lines) and 16 randomly selected e-mail correspondents (blue lines). (B) Cumulative distribution of rescaled τ 's on logarithmic and linear (inset) axes. The interval time $\tau_k = t_{k+1} - t_k$ is rescaled by the average τ expected during the interval $[t_k, t_{k+1}]$, $\langle \tau_k \rangle = (t_{k+1} - t_k) / \int_{t_k}^{t_{k+1}} \rho(s) ds$. By the time-rescaling theorem (30), the resulting rescaled τ distribution is given by the expected τ distribution for a homogeneous Poisson process with unit rate $P(\tau) = e^{-\tau}$ (black dashed line). We only consider interval-event times $\tau > 0$ for letter correspondence.

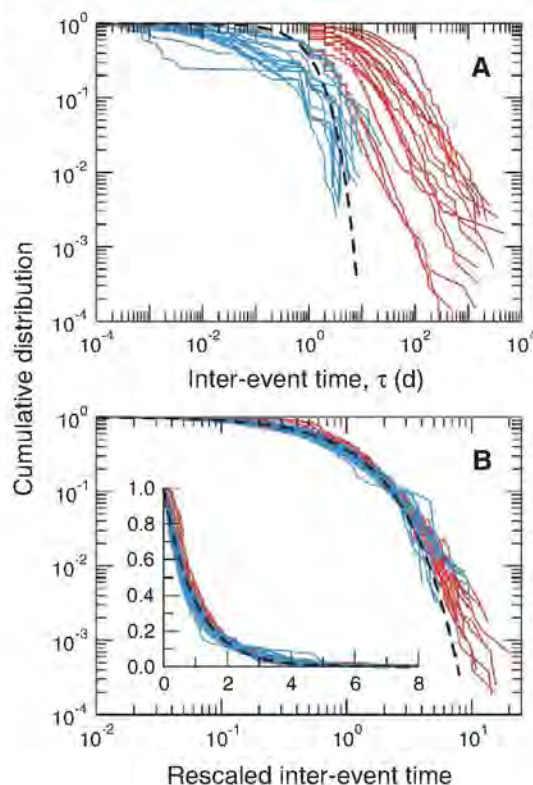


Table 1. Summary of the letter correspondence records and hypothesis testing results for the 16 individuals under consideration, ordered chronologically. For each individual, we note the time period and duration of the letter correspondence records, the total number of letters sent, the number of time segments with at least 10 letters per time segment, the 95% CI bounds of the corresponding binomial model with $P = 0.05$, and the number of rejections of the cascading Poisson process based on our Monte Carlo hypothesis testing procedure. The number of Monte Carlo hypothesis testing rejections is within the 95% CI bounds for all 16 individuals, indicating that this model cannot be rejected for any individual's letter correspondence patterns. We have conducted the same analysis for three alternative models; we find that a cascading Poisson process provides the most parsimonious and statistically consistent explanation of the data [SOM text S3].

Individual	Time period	Duration (years)	Number of letters	Number of segments	95% CI	Number of rejections
Francis Bacon	1574–1626	53	443	19	[0,3]	3
James H. Leigh Hunt	1790–1859	70	408	25	[0,3]	1
Charles Darwin	1822–1882	61	6785	52	[0,5]	4
Anna Brownell Jameson	1833–1860	28	119	8	[0,2]	1
Friedrich Engels	1833–1895	63	369	24	[0,3]	1
Robert E. Lee	1835–1870	36	282	10	[0,2]	0
Karl Marx	1837–1882	46	469	25	[0,3]	1
Henry Irving	1852–1905	54	1205	35	[0,4]	0
Sigmund Freud	1872–1939	68	3130	49	[0,5]	2
Marcel Proust	1879–1922	44	668	25	[0,3]	2
H. G. Wells	1895–1946	52	422	16	[0,2]	0
Albert Einstein	1896–1955	60	10,319	54	[0,6]	2
Carl Sandburg	1898–1966	69	1894	37	[0,4]	2
Arnold Schoenberg	1902–1951	50	6899	47	[0,5]	3
Ernest Hemingway	1909–1961	53	1934	42	[0,5]	5
Stan Laurel	1924–1964	41	685	17	[0,3]	1

demonstrate that the origin of the heavy-tailed τ distribution is a mixture of distributions with different time scales (Fig. 2, C to E).

Our findings enable us to address a crucial question: Do e-mail and letter correspondence belong to different universality classes (20)? Because the same mechanistic model is capable of describing both e-mail and letter correspondence, we can answer this question in the negative. We demonstrate the underlying similarity of both correspondence activities by rescaling and collapsing the τ distributions for 16 randomly selected e-mail correspondents (29) for which we have model parameter estimates (14) and the 16 letter correspondents studied here (Fig. 3). The rescaled τ distributions agree with theoretical expectations (30), demonstrating that the same exponential statistical law is indeed capable of describing both correspondence patterns.

Only by understanding and validating the underlying mechanisms can we appropriately rescale e-mail and letter correspondence to reveal their underlying similarity. Unlike critical phenomena, the universality here does not arise from the irrelevance of idiosyncrasies but rather from the fact that these two different modes of communication are governed by the same mechanisms. This insight is not apparent just from studying the asymptotic scaling of an empirical distribution obtained from an individual; one cannot simply infer that different scaling exponents necessarily imply different mechanisms.

Our results therefore raise important questions about the nature of universality in complex phenomena in general, and in human correspon-

dence in particular. Perhaps the most common universal statistical law is due to the central limit theorem: Sums of variates with finite fluctuations converge to a Gaussian distribution. When confronted with statistical patterns that are non-Gaussian, one is tempted to surmise that the system's fluctuations are not finite. In analogy to physical systems, the recurrence of power law dependencies with similar exponent values in biological or social systems is frequently hypothesized to arise from the operation of these systems near critical points, where particular details of the system become irrelevant.

A less explored hypothesis, as exemplified here, is that heavy-tailed distributions emerge as a result of nonstationarities in the absence of criticality (14, 31). Our study demonstrates that human correspondence can be accurately modeled as a cascading nonhomogeneous Poisson process: a noncritical process. This process gives rise to heavy-tailed statistics but not to power law statistics characterized by critical exponents. Instead, the correspondence patterns of each individual are uniquely characterized by the parameters of our model (32); the process is universal, but the parameters are not.

Indeed, we hypothesize that the cascading Poisson process, which formally incorporates the effects of the circadian cycle, task repetition, and changing needs, may accurately describe many other aspects of human activity. The circadian cycle has physiologic impact and may thus affect numerous human behaviors, from eating habits to commuting routines. Task repetition is similarly important because of the increased efficiency

it enables; once an individual makes one purchase at a mall, it is easier to make other purchases within that mall during the same trip than it is to return to the mall the following day. As one ages and changes roles, it is not hard to imagine that the extent to which the circadian cycle and task repetition influence an individual's activity might change over time. It is therefore plausible that the cascading Poisson processes presented here could be generalized to account for different types of activities, each with its own evolving parameters.

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Supporting Online Material

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Materials and Methods

SOM Text
Figs. S1 to S5
Tables S1 to S3
References

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Antennal Circadian Clocks Coordinate Sun Compass Orientation in Migratory Monarch Butterflies

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During their fall migration, Eastern North American monarch butterflies (*Danaus plexippus*) use a time-compensated Sun compass to aid navigation to their overwintering grounds in central Mexico. It has been assumed that the circadian clock that provides time compensation resides in the brain, although this assumption has never been examined directly. Here, we show that the antennae are necessary for proper time-compensated Sun compass orientation in migratory monarch butterflies, that antennal clocks exist in monarchs, and that they likely provide the primary timing mechanism for Sun compass orientation. These unexpected findings pose a novel function for the antennae and open a new line of investigation into clock-compass connections that may extend widely to other insects that use this orientation mechanism.

Eastern North American monarch butterflies, *Danaus plexippus*, undergo one of the most magnificent long-distance mi-

grations observed in animals. Each fall in the northern United States and southern Canada, migratory monarchs travel distances up to 4000 km

to arrive at their overwintering grounds in central Mexico (1, 2). The navigational abilities of the migrants include the use of a time-compensated Sun compass (3–5). Previous studies show that a circadian clock provides the internal timing device that allows the butterflies to correct their flight orientation, relative to skylight parameters, and to maintain a southerly flight bearing as the Sun moves across the sky during the day (3–5).

A distinctive circadian clock mechanism has been recently elucidated in the monarch butterfly (6). It relies on a negative transcriptional feedback loop that involves the transcription factors CLOCK (CLK) and CYCLE (CYC), which drive the expression of *period* (*per*), *timeless* (*tim*), and a vertebrate-like *cryptochrome* designated *cry2*. The translated PER, TIM, and CRY2 proteins

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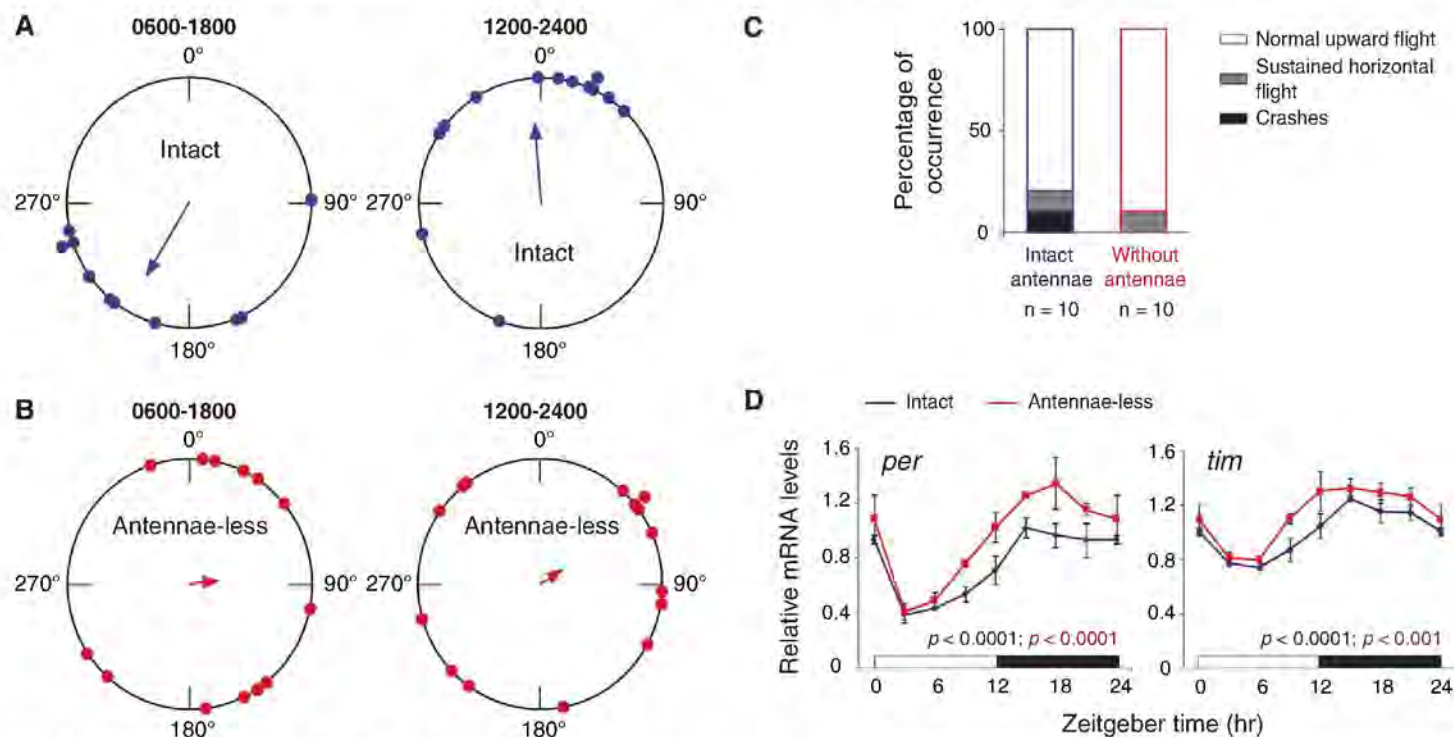


Fig. 1. Antennae are necessary for time-compensated sun compass orientation. (A) Flight orientation of intact migrants under different lighting conditions. Butterflies were flown between 1100 and 1500 hours from 24 September to 18 October 2008. The large circle represents the 360° of possible directions (0° is north); small solid circles on the perimeter represent the flight orientation of individual butterflies. The arrow indicates the mean vector; arrow length, *r* value. Left, orientation data of butterflies in LD. Right, orientation

data of butterflies in 6-hour-delayed LD. (B) Orientation of antennaeless migrants under the different lighting conditions. (C) Free-flight behavior of intact migrants (left bar) and those without antennae (right bar). (D) Temporal profiles of *per* and *tim* mRNA levels in brains of monarchs with antennae (blue) and without antennae (red). Values are mean $\pm$ SEM of three brains. Points at CT0 are replotted at CT24 to show 24-hour trend. Horizontal bars: open, light; black, darkness. *P* values, one-way analysis of variance (ANOVA).

form complexes in the cytoplasm and, after the appropriate time delay, translocate back into the nucleus where CRY2 represses CLK:CYC-mediated transcription (6–8). A *Drosophila*-like CRY also exists in the butterfly, designated CRY1, which functions as a blue light photoreceptor to synchronize (entrain) the circadian clockwork to the prevailing light-dark conditions (6). Four cells in the dorsolateral region of the central brain (the pars lateralis) house the major circadian clocks in butterfly brains (6, 9).

Because circadian rhythms in locomotor activity and the timing of adult eclosion in insects such as silkworms (10) and *Drosophila* (11) are under the control of brain clocks, it has been assumed that the clock involved in time-compensated sun compass orientation in monarchs is also located in the brain (6, 9, 12). This assumption has never been examined directly. The location of the sun compass, on the other hand, is more firmly established. On the basis of electrophysiological studies

in locusts and crickets (13, 14) and genetic studies in *Drosophila* (15), it resides in the central complex, a midline structure in the brain of insects.

In addition to the brain, circadian clocks are also found in the antennae of insects (16–19) and likely exist in the antennae of monarch butterflies. Insect antennal clocks are believed to modulate olfactory reception within the antennae themselves (20, 21), and there has been scant evidence that antennal clocks directly influence brain mechanisms. However, Urquhart presented anecdotal evidence almost 50 years ago suggesting a role of the antennae in the flight orientation of migratory monarchs (2) that was not pursued. In view of this historical observation and our interest in Sun compass mechanisms (12), we rigorously examined the role of the antennae in Sun compass orientation.

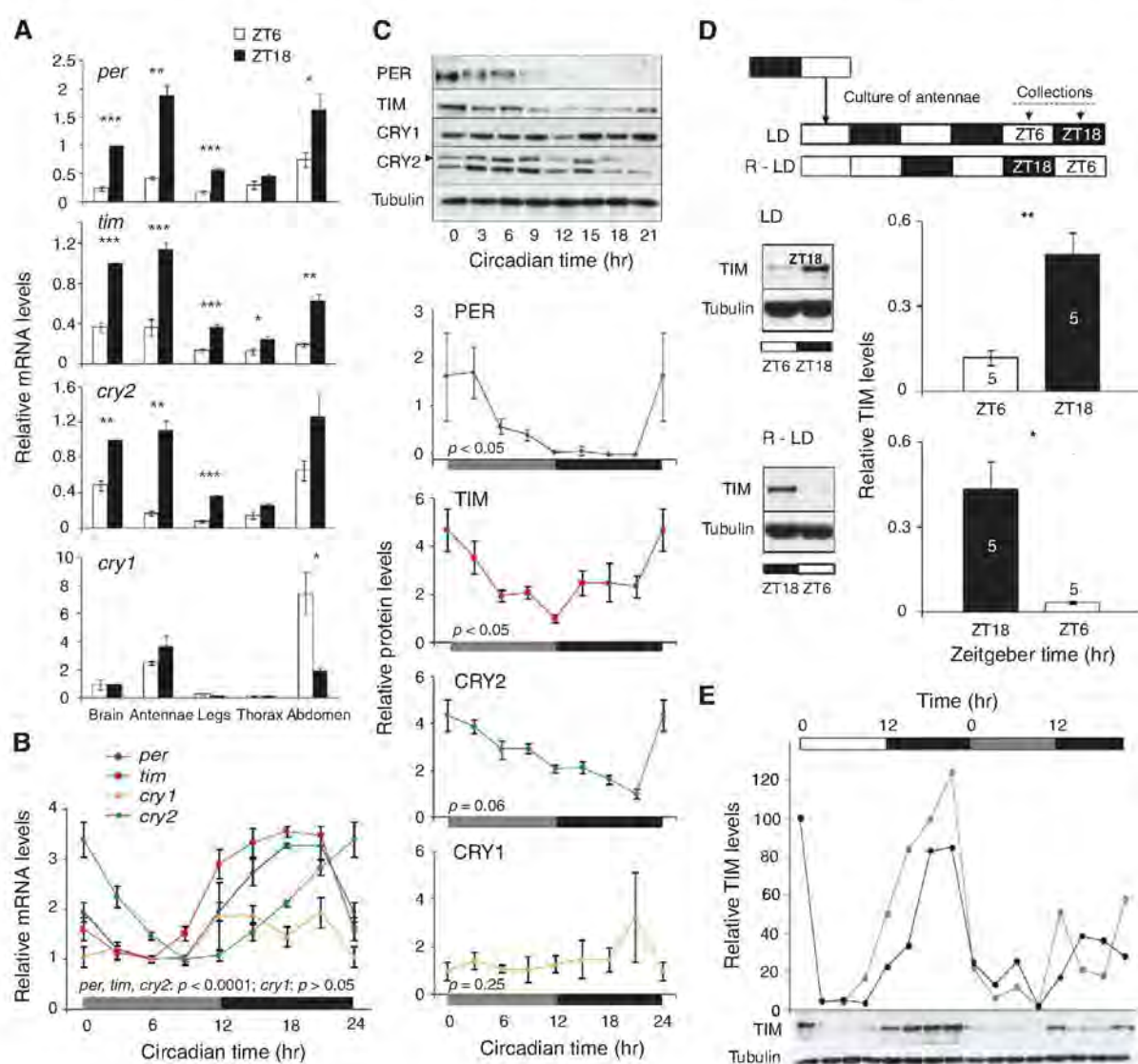
To begin, we compared time-compensated Sun compass orientation of intact migrants with migrants whose antennal flagellum had been surgically removed (fig. S1) (22). Both intact and

antennaeless migratory monarchs were housed indoors in either a 12-hour light:12-hour dark (LD) cycle that was timed to coincide with prevailing lighting conditions or a 6-hour-delayed LD cycle. Six to 8 days later, the butterflies housed in either lighting cycle were tethered, and over the next 26 days individual flight direction and group orientation were examined in butterflies flown outdoors in a flight simulator (22, 23) (fig. S2).

Intact monarch migrants housed under LD conditions exhibited directional flight that was oriented as a group significantly to the southwest with a mean vector (α) of 211° ($n = 10$, $r = 0.67$, $P < 0.01$; Rayleigh test; Fig. 1A left), in close agreement with previous reports (3, 4, 24). The group of intact migrants housed under the 6-hour-delayed LD cycle were also oriented significantly but in the northwesterly direction, with an α of 355° ($n = 13$, $r = 0.63$, $P < 0.005$; Fig. 1A, right). The clockwise shift in the direction of orientation in the 6-hour-delayed LD group, relative to the LD

Fig. 2. Circadian clocks in monarch antennae.

(A) Clock gene expression in monarch tissues. Tissues were collected at ZT6 (white) and ZT18 (black). Values are normalized to those in the brain at ZT18 and are mean $\pm$ SEM of four animals. P values, Student's t test: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. (B) Clock gene mRNA profiles in antennae. Values are relative to the minimal level for each gene and are the mean $\pm$ SEM of four antennae. Points at CT0 are replotted at CT24. Horizontal bars: gray, subjective day; black, subjective night. P values, one-way ANOVA. (C) Circadian profiles of clock protein abundance in antennae. Top, representative autoradiographs in DD. Arrowhead, CRY2 band; the lower band is nonspecific, as shown previously (6). Bottom four graphs, quantification of relative protein levels. Values are normalized to the minimal level of protein expression and are mean $\pm$ SEM of three or four antennae. P values, one-way ANOVA. (D) Light sensitivity of antennae in culture. Top, experimental scheme in LD or in phase-reversed LD (R-LD). Arrows, collection times. Bottom, Western blot analyses. Left, representative blots; right, quantifications. Open bars, mid-light; black bars, mid-dark. Values are mean $\pm$ SEM of five antennae. P values, Student's t test: ** $P < 0.01$ and * $P < 0.05$. (E) Daily and circadian patterns of TIM abundance in two sets of cultured antennae (gray and black lines, respectively). Top, lighting conditions. Bottom, representative Western blot.



nae. P values, Student's t test: ** $P < 0.01$ and * $P < 0.05$. (E) Daily and circadian patterns of TIM abundance in two sets of cultured antennae (gray and black lines, respectively). Top, lighting conditions. Bottom, representative Western blot.

group, was expected for a time-compensated Sun compass that has been delayed by several hours. However, the magnitude of the difference between the two groups (a clockwise shift of 144° ; $F_{1,21} = 31.92$, $P < 0.0001$; Watson-Williams test) was greater than expected for the 6-hour shift ($\leq 132^\circ$; the speed of the Sun's azimuth varied from 14° to 22° per hour during the study period) but within the range of directions found in a large number of phase-delayed migrants (24).

Remarkably, group flight was disoriented in the antennaeless monarchs studied under either lighting cycle (Fig. 1B). Individual antennaeless migrants housed under either LD or the 6-hour-delayed LD cycle each exhibited significant directional flight. However, orientation of each of the two groups was randomly distributed over the 360° of direction ($n = 13$, $r = 0.23$, $P > 0.05$ for the LD group and $n = 15$, $r = 0.209$, $P > 0.05$ for the 6-hour-delayed LD group) (Fig. 1B). Antennaeless migrants flew as strongly and consistently as intact butterflies in the flight simulator, and the proportion of antennaeless migrants eliminated from analysis because of nondirectional flight did not differ from the proportion of intact migrants (22).

Because the antennae have been shown to mediate flight stability in moths through mechanosensors located at the base of the antennae (25), we also analyzed the effect of antennal flagellum amputation on the free-flight performance of migrant monarchs (22). We found that the majority of intact and antennaeless migrants exhibited normal upward flight (8/10 and 9/10, respectively) (Fig. 1C). Thus, the effect of antennal amputation on flight orientation of migrating monarch butterflies was not the consequence of disrupted flight stability. Taken together, our results show that the antennae are necessary for time-compensated Sun compass orientation in migratory monarch butterflies.

The disorientation of flight behavior in the antennaeless butterflies suggested that the timing component of the time-compensated Sun compass mechanism was disrupted when antennal input was lacking. Is it possible that the antennae are necessary for the proper workings of the molecular clocks in the brain? To test this, we examined the temporal patterns of clock gene expression in the brains of butterflies with and without antennae. With use of the quantitative real-time polymerase chain reaction (qPCR), we analyzed the temporal expression patterns of the clock genes *per* and *tim* (22); these genes were chosen because they exhibit the most robust mRNA cycling among the clock genes previously studied in monarch heads (6). The butterflies were studied in LD to match the condition used for the flight orientation experiments.

The levels of *per* and *tim* mRNA in brains of intact and antennaeless butterflies cycled in phase (Fig. 1D), as previously described in monarch heads and in DpN1 cells, a monarch butterfly cell line that contains a light-driven clock (6). Thus, compared to the brains from butterflies with in-

tact antennae, the relative timing of *per* and *tim* mRNA levels to the LD cycle were unaltered in antennaeless butterflies. These results suggest that the brain clocks are functioning in synchrony in LD without attached antennae and raise the interesting prospect that the clock for time compensation may actually reside in the antennae and not in the brain.

Accordingly, we next surveyed rhythmic clock gene mRNA and protein expression in the antennae, as well as in other peripheral tissues (legs, thorax, and abdomen) of monarch butterflies. By using qPCR, we found that the mRNA amounts of *per*, *tim*, and *cry2* were significantly lower at mid-light [Zeitgeber time (ZT)6] than at mid-dark (ZT18) in the antennae and the legs, similar to those in the brain (Fig. 2A). The expression of *tim* was also significantly reduced at ZT6 compared with ZT18 in the thorax and the

abdomen, and *per* expression showed a similar oscillation in the abdomen. There were no significant differences in *cry1* mRNA amounts in most tissues examined (Fig. 2A). At the protein level (22), the antenna was the only peripheral tissue of those examined to express clock protein abundance patterns similar to those found in the brain (fig. S3).

Focusing on antennae, a more detailed temporal analysis showed that *per*, *tim*, and *cry2* mRNA levels exhibited robust circadian rhythms in constant darkness (DD) (Fig. 2B), similar to those previously described in monarch brains (Fig. 1D) and/or in DpN1 cells (6). PER and TIM also exhibited significant circadian oscillations in abundance (Fig. 2C). In addition, PER showed temporal changes in electrophoretic mobility corresponding to changes in phosphorylation (6) (Fig. 2C). CRY2 showed a temporal trend in abundance

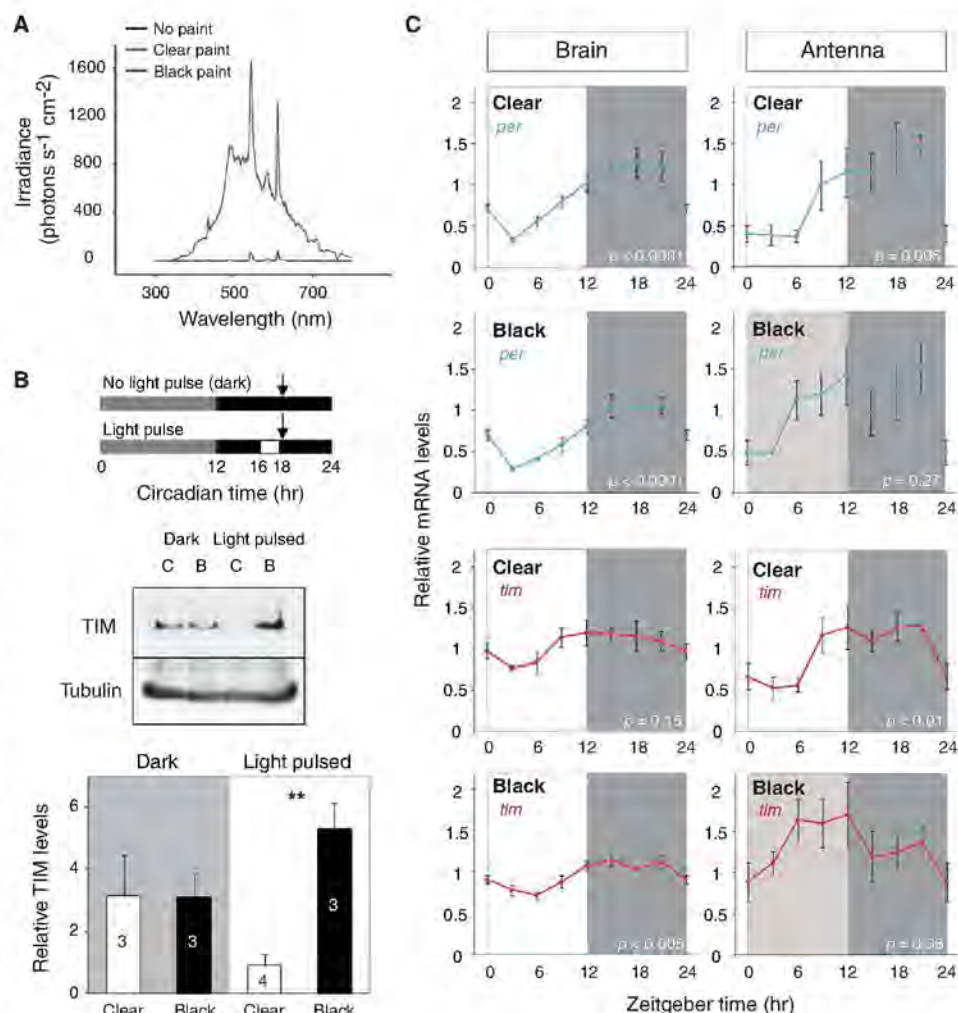


Fig. 3. Blinding antennal clocks alters their timing. (A) Irradiance curves for different painting conditions. Light measurements were taken under full-spectrum light through plastic that was either painted or not. (B) Light sensitivity of TIM abundance. Top, experimental paradigm. Painted antennae were harvested at CT18 (arrows). Middle, blot of TIM levels from pooled antennae painted clear (C) or black (B) from butterflies in dark or light pulsed. Bottom, quantifications. Values are mean $\pm$ SEM of three or four antennae. White bars, clear-painted antennae; black bars, black-painted antennae. P values, Student's *t* test: ** $P < 0.005$. (C) Temporal patterns of *per* and *tim* expression in brain (left column) and antenna (right column) from butterflies with the antennae painted clear or black. Values are mean $\pm$ SEM of three animals, except for the three points without error bars that represent the mean of two animals. Box shading: open, light; dark gray, night; and light gray, subjective day. P values, one-way ANOVA.

that was not significant (Fig. 2C). Circadian cycling of mRNA and protein levels of these core clock components *in vivo* suggests the presence of circadian clocks in the monarch butterfly antenna.

To show that the monarch antennae actually house light-entrained and tissue-autonomous circadian clocks, we examined whether the antennal clocks are reset by light and continue to oscillate when explanted *in vitro* (22). The light sensitivity of isolated antennae was evaluated by maintaining antennae in culture in two oppositely phased LD cycles and probing TIM abundance by Western blot. In both lighting conditions, TIM expression was significantly lower during the light phase (at ZT6) than in the dark (at ZT18) (Fig. 2D). These data show that the LD oscillation in TIM abundance persists *in vitro* in a phase-appropriate manner, suggesting that the antennal clocks can be directly entrained by light, even when disconnected from the brain. We also investigated the ability of the antennae to maintain self-sustained circadian oscillations by analyzing the temporal abundance of TIM in LD and during the first day in DD from individual antennae maintained in culture. TIM abundances oscillated in LD and continued to oscillate, although with reduced amplitude, on the first day in DD (Fig. 2E). Thus, monarch antennae possess light-sensitive circadian clocks, which could function independently from the brain as time-compensation components for sun compass orientation.

If antennal clocks are involved in Sun compass orientation in migrants, then altering their rhythmicity *in vivo* should alter time-compensated sun compass orientation. Blocking light input to antennal clocks should alter their rhythmicity in two ways. First, antennal clocks would continue to oscillate but would gradually drift out of their normal phase relationship with the prevailing lighting cycle (i.e., “free-running” clocks). Second, after several days without light input, the individual free-running clocks would eventually desynchronize from each other because of the innate difference in free-running period length (26).

To prevent light input to intact antennae, we painted the flagellum with an enamel-based black paint (fig. S1) (22), which blocked antennal perception of full-spectrum light (from 300 nm to 800 nm; Fig. 3A); the control, enamel-based clear paint, did not reduce either the intensity or wavelengths of light that could pass through the antenna (Fig. 3A). We verified the efficiency of black paint to block light input *in vivo* by examining the light-induced decline in TIM abundance in painted antennae. As expected, clear- and black-painted antennae in DD had similar TIM abundance during mid-subjective night (the period the lights normally would have been off in LD) (Fig. 3B). However, when both groups were exposed to a 2-hour light pulse from [circadian time (CT)16] to CT18, TIM abundance was substantially lower in the clear-painted antennae

compared with that of antennae painted black (Fig. 3B). Thus, black paint blocks light input to the antennal clocks.

Light sensitivity of the antennae is unlikely to be mediated by opsins because QPCR of the three opsin genes in monarchs [ultraviolet, blue, and long wavelength (9)] showed that they were not detected in the antennae (fig. S4). CRY1 is likely the photoreceptor for the light-input pathway to the antennal clocks and for causing TIM degradation (6). In contrast to *Drosophila* CRY, monarch CRY1 is not degraded by light in either the brain (6) or the antennae (fig. S5). However, knocking down CRY1 expression by RNA interference in DpN1 cells blocks the ability of light to degrade TIM, showing that the monarch CRY1 is a light sensor (6).

To examine how the rhythmicity of antennal clocks is altered by black paint, we quantified by QPCR the expression of the clock genes *per* and *tim* from both clear- and black-painted antennae of butterflies maintained in LD for 11 days after painting (Fig. 3C). In clear-coated antennae, *per* and *tim* mRNA amounts exhibited robust daily rhythms that were in phase with each other. In the same animals, *per* was also rhythmically expressed in the brain, with the phase of the oscillation similar to that found in the antennae. The daily pattern of *tim* in the brain, however, was similar but not significantly rhythmic. The lack of a significant oscillation for *tim* was likely due to the combined effects of individual variation and the shallow

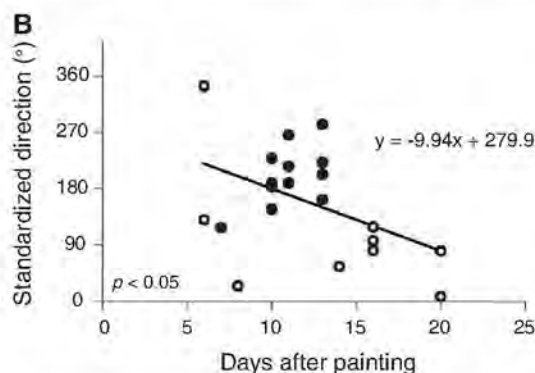
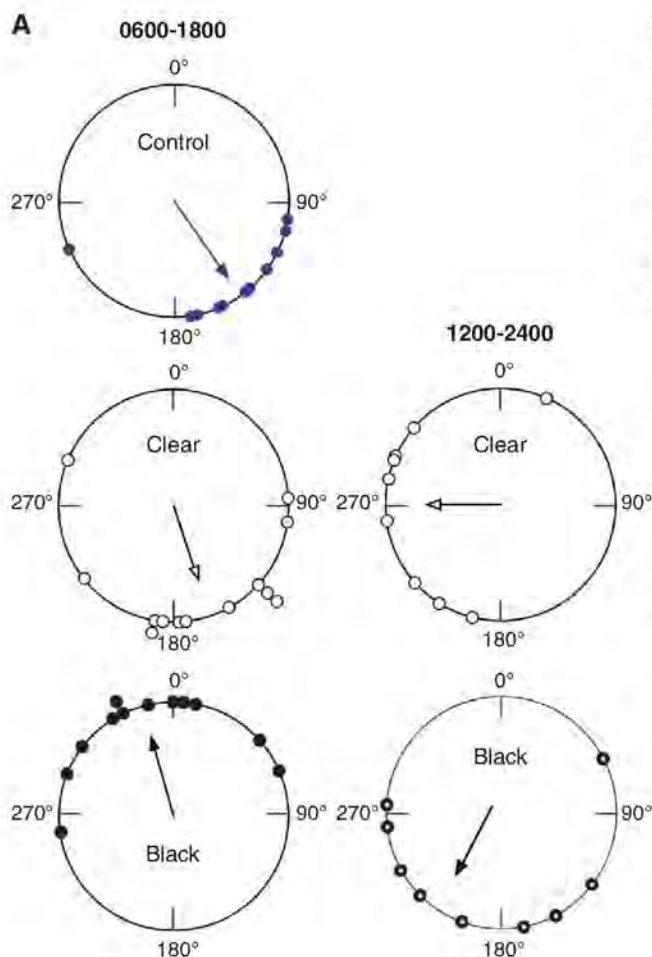


Fig. 4. Blinding antennal clocks alters Sun compass orientation. (A) Flight orientation of migrant butterflies with intact antennae (control, top) and with antennae painted clear (middle) or black (bottom). Butterflies were flown between 1100 and 1500 hours from 20 October to 16 November 2008. Left, butterflies housed in LD. Right, butterflies housed in 6-hour-delayed LD. (B) Relationship

between orientation angle and day of study. Individual orientation directions were standardized to the mean vector of control butterflies ($144^\circ = 360^\circ$) and assumed to be drifting from the mean in a counterclockwise direction over time. Thus, orientation angles are expected to decrease with increasing days after painting, from 360° to 0° to -360° for two revolutions. One orientation direction on day 16 was calculated to be -82° [for the 62° value in (A), lower right]. The absolute value of 82° was used so that all orientations could be tested from 360° to 0° . Black dots, LD 0600 to 1800; open dots, 1200 to 2400. *P* value, linear regression analysis.

amplitude rhythms normally found in the brain (Fig. 1D right) (6). Predictably, *per* and *tim* mRNA amounts were not significantly rhythmic in the black-painted antennae and exhibited peak amounts occurring earlier and for a broader duration than in the clear-painted antennae (Fig. 3C), whereas these genes cycled normally in the brains of the same butterflies.

Painting the antennae black thus appears to specifically block LD entrainment of the antennal clocks. The lack of overall rhythmicity observed in black-painted antennae is likely due to desynchrony among the free-running clocks after 11 days in virtual DD. This apparent arrhythmicity could be due to desynchrony of antennal clocks within the antenna of individual butterflies, between the two antennae, among the antennae of the different butterflies, or a combination of these effects. Thus, sufficient synchrony among free-running clock gene oscillations may exist after several days to synchronize group flight orientation (see below).

To test a potential role of antennal clocks in time-compensated Sun compass orientation of migratory monarchs, we analyzed the flight orientation of migrants with either clear- or black-painted antennae housed in LD or placed from LD into the 6-hour phase-delayed LD cycle after painting. We found that the control migrants without antennal painting and migrants with clear-painted antennae both oriented significantly to the south to southeast with α values of 144° and 162° , respectively ($n = 11$, $r = 0.80$, $P < 0.0001$ and $n = 13$, $r = 0.66$, $P < 0.005$; Fig. 4A). The mean flight orientation did not differ significantly between groups ($F_{1,22} = 0.77$, $P > 0.05$). Such a south/southeasterly orientation direction has been reported previously for flight simulator studies (27) and free-flight studies late in the season (28). The migrants in our study oriented in the southwesterly direction at the beginning of the fall (Fig. 1 top left) but oriented to the southeast later in the season (Fig. 4A left). Nonetheless, migrants with clear-painted antennae housed under 6-hour-shifted LD showed the appropriate shift in their orientation toward the west ($\alpha = 269^\circ$, $n = 9$, $r = 0.63$, $P < 0.05$; Fig. 4A right); the direction and magnitude of the group orientation differences between the two groups with clear-painted antennae (a clockwise shift of 107° , $F_{1,20} = 17.48$; $P < 0.001$) were those expected for a time-compensated Sun compass delayed by 6 hours. Thus, although clear-painted antennae lack olfactory reception (fig. S6), they have normal light reception for entraining antennal clocks, and, correspondingly, those migrants show proper time-compensated Sun compass orientation.

A completely different situation was found for flight orientation in the migrants with black-painted antennae. As a group, those migrants housed under LD oriented significantly to the north to northwest ($\alpha = 344^\circ$, $n = 12$, $r = 0.73$, $P < 0.001$; Fig. 4A left), an orientation direction that was 182° different from that of the group of migrants with clear-painted antennae

($F_{1,23} = 61.17$, $P < 0.00001$). Migrants with black-painted antennae and housed under the 6-hour-shifted LD cycle did not exhibit significant group orientation ($n = 9$, $r = 0.5$, $P > 0.05$; Fig. 4A right), but there was a trend to orient to the southwest. A second difference between the group maintained in LD and the 6-hour-shifted LD group was related to the interval from antennal painting to analysis in the flight simulator. Although the butterflies were flown randomly, retrospectively, the groups differed in distribution over time since painting (fig. S7).

If the altered flight orientation directions of the migrants with black-painted antennae were a general reflection of the timing of free-running antennal clocks, there should be a correlation between the day of study and the direction of oriented flight; that is, there should be either a progressive increase or a decrease in the angle of orientation with increasing days of study after antennal painting. Because a short free-running period length in DD had been described previously for the timing of adult eclosion behavior in monarchs [figure S3B in (6)] and the *per* and *tim* mRNA patterns measured after 11 days in black-painted antennae were advanced in their peak amounts (Fig. 3C), we calculated the drift in orientation angle over the 14 days of study in a counterclockwise direction relative to mean orientation of control butterflies. Consequently, we observed a significant linear relationship between day of study and orientation angle (Fig. 4B). The slope of the regression line ($y = -9.9x + 279.9$) predicted a free-running period length for the antennal clocks of 23.3 hours, in accordance with the short free-running period found for adult eclosion.

These flight simulator data are consistent with a free-running timing mechanism in the black-painted antennae that influences sun compass orientation. The orientation findings in migrants with black-painted antennae contrast with those of the antennaeless butterflies in which antennal clocks have been removed and no residual group orientation is apparent (Fig. 1B), although these migrants were studied later after antennal removal (fig. S2).

The altered flight directions of migrants with black-painted antennae could also reflect the combined effects of free-running antennal clocks and entrained brain clocks on sun compass orientation. Indeed, flight orientation of migrants with black-painted antennae differed between the LD group and the 6-hour-shifted LD group (Fig. 4A, bottom left and right), suggesting a role of brain clocks. Thus, circadian information from the antennae and the brain may be integrated downstream from the actual clocks themselves, perhaps at an integration site somewhere in the central complex or its output pathways controlling motor behavior.

We found that the antennae are necessary for proper time-compensated sun compass orientation in migratory monarch butterflies. Our results are consistent with a major role of antennal clocks in the timing of Sun compass orientation in migratory monarchs. The antennae may function

alone, without any influence from brain clocks, or antennal output may influence the integration of timing information from brain circadian clocks within the Sun compass structure or at the level of its output pathways. Both possibilities suggest the existence of a crucial but hitherto unknown neural circuit between the antennae and the central complex system.

The role of the antennae in the clock-compass circuitry underlying sun compass orientation could have broad implications, because a similar process may extend to other insects (such as bees, ants, and locusts) that use this orientation mechanism. Furthermore, our results add to the growing list of important nonolfactory functions (e.g., gravity, wind, and sound sensing) housed in the antennae of insects (25, 29, 30).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5948/1700/DC1
Materials and Methods

Figs. S1 to S7

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Optimizing Influenza Vaccine Distribution

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The criteria to assess public health policies are fundamental to policy optimization. Using a model parametrized with survey-based contact data and mortality data from influenza pandemics, we determined optimal vaccine allocation for five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs. We find that optimal vaccination is achieved by prioritization of schoolchildren and adults aged 30 to 39 years. Schoolchildren are most responsible for transmission, and their parents serve as bridges to the rest of the population. Our results indicate that consideration of age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines. We also found that previous and new recommendations from the U.S. Centers for Disease Control and Prevention both for the novel swine-origin influenza and, particularly, for seasonal influenza, are suboptimal for all outcome measures.

Vaccination is the principal strategy for reducing the disease burden of many infectious diseases. The evaluation of vaccination policies before their implementation is essential to allocate resources and to minimize disease burden. Outcome measures applied to quantify the success of a vaccination program are fundamental to this evaluation.

Vaccination has the indirect benefit of decreasing transmission, thereby reducing the infection risk even for those who have not been vaccinated. Mathematical modelers of influenza transmission take into account this indirect protection but typically only evaluate outcomes using deaths or infections averted (1–4). By contrast, ethicists focus on the debate regarding the outcome measure that should be used to prioritize influenza vaccination. Ethicists have proposed outcome measures that incorporate valuation based on the ages of victims (5–7). For example, in terms of years of life lost, children would be valued over adults. Young adults are prioritized by measures based on surveying public values attributed to people at different ages (7, 8). Another alternative outcome measure is the economic cost, including age-specific mortality costs (9, 10). However, ethicists and health economists neglect the transmissible nature of influenza in making their recommendations about which age groups should be targeted for interventions (11). For example, children are responsible for a disproportionate amount of influenza transmission (12–19), which affects age-specific vaccination policies (20–22). Thus, it is necessary to take into account transmission dynamics to determine optimal vaccination policy for the community overall, which depends on which of the different outcome measures is used.

Levels of annual influenza vaccination were estimated from the 2007 National Health Interview Survey (23) as 34% for people aged 0 to 4,

20% for those aged 5 to 19, 17% for those aged 20 to 49, 35% for those aged 50 to 64, and 63% for those older than 64 years (fig. S15), totaling about 85 million vaccine doses. The influenza vaccine must be updated annually to keep pace with

the antigenic evolution of influenza. In addition, zoonosis can lead to the emergence of influenza subtypes, such as the novel swine-origin influenza virus. Consequently, manufacturing of influenza vaccine follows a tight schedule to achieve sufficient doses (24). This schedule is also vulnerable to disruptions, as evidenced by the vaccine contamination that left the United States short on doses in 2004 to 2005 (25). The World Health Organization recently announced that the unusually slow growth of swine-origin H1N1 in chicken eggs may cause shortfalls in current production of vaccine this year (26). When vaccine availability is limited or when vaccine efficacy is low, optimal allocation of vaccines is imperative. Nonetheless, vaccine allocation can also be improved when vaccine is plentiful and highly efficacious. We evaluated current vaccine allocation policies based on the optima derived from multiple outcome measures. We also compared the outcome measures when vaccine availability and efficacy vary, an understanding of which will be fundamental to

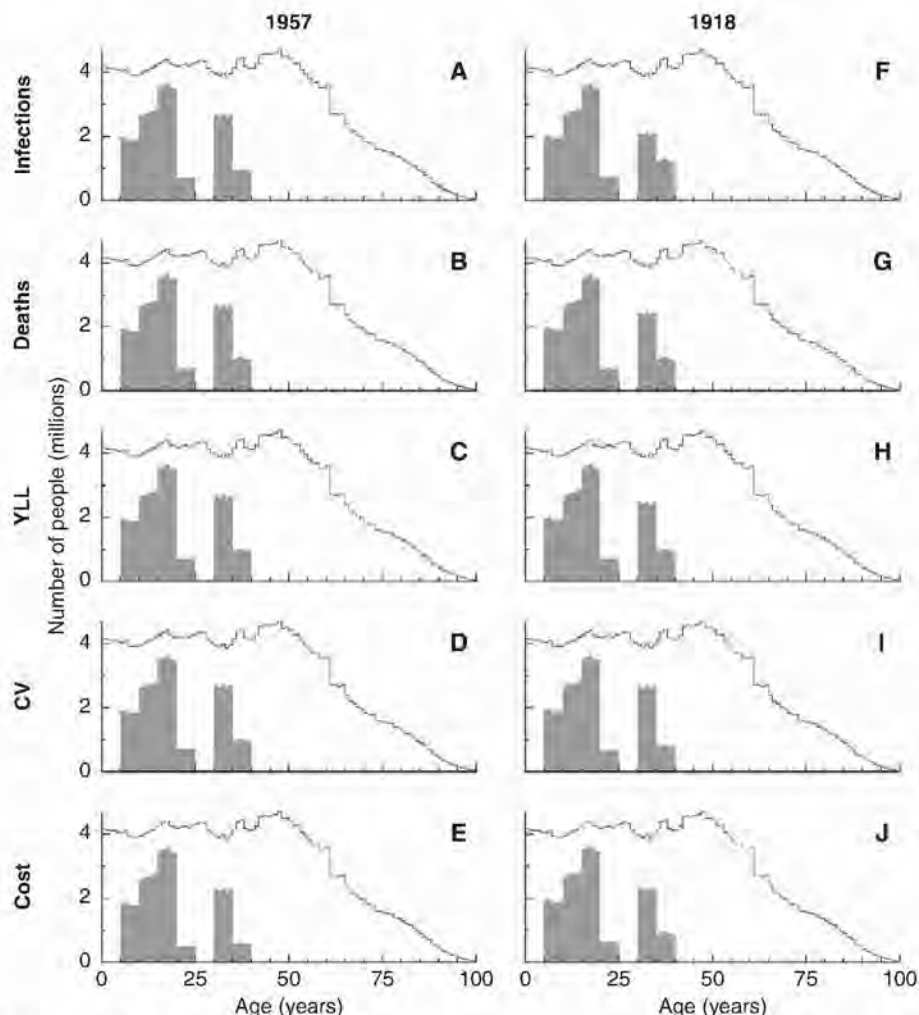


Fig. 1. (A to J) Optimal age-specific vaccine allocation with just enough vaccine doses for eradication. For an outbreak with the 1957 mortality pattern, 63 million vaccine doses lead to eradication, whereas 62 million vaccine doses were required for eradication of an outbreak with the 1918 mortality pattern. The line indicates the 2007 U.S. population by age, and the shaded area is the proportion of each age group vaccinated under the optimal strategies for each outcome measure (labeled at the far left). YLL is years of life lost.

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the allocation of vaccine doses during the current outbreak of swine-origin influenza.

To evaluate vaccination strategies for the different outcome measures, we developed an age-structured model that incorporates transmission dynamics (27). We applied an optimization routine that identifies the optimal strategy for each outcome measure. Rather than comparing the efficacy of just a few specific vaccination policies, as is often done in modeling, our routine allows us to find the optimal vaccine distribution, essentially evaluating all possible age-based vaccination policies. We compared patterns of influenza A transmission and mortality in the United States, parametrized with survey-based contact data (28) and mortality data from the 1957 and 1918 pandemics. These two pandemics had qualitatively different patterns of mortality. Both of these pandemics infected 25 to 30% of the U.S. population, but there were about 6 times as many deaths from the 1918 pandemic in a 40% smaller population, a 10-fold difference in per capita mortality (29). The elderly suffered the greatest mortality in the 1957 pandemic, whereas infants and young adults suffered the highest mortality during the 1918 pandemic (fig. S2) (29–31). The 1957 mortality pattern is representative both of seasonal influenza and of the 1968 pandemic. Because of the uncertainty of the mortality patterns of future outbreaks, we considered mortality based on both the 1957 and 1918 pandemics.

The model tracks 17 age groups for the 2007 U.S. population: ages 0, 1 to 4, 5 to 9, 10 to 14, ..., 70 to 74, and 75 and older. For the duration of the incubation period, we used 1.2 days and 4.1 days for the duration of the infectious period (32). Sensitivity analysis was also performed with regard to vaccine efficacy, but baseline age-dependent vaccine efficacy against infection was 80% for 0 to 64-year-olds and 60% for those 65 and older (4, 33), and age-dependent vaccine efficacy against death, if infected, was 75% for 0 to 19-year-olds, 70% for 20- to 64-year-olds, and 60% for those 65 and older (table S1) (4, 34). We assumed that the basic reproductive number (R_0), defined as the number of secondary cases caused by a single infective case in a completely susceptible population (35), was $R_0 = 1.4$, as estimated for the novel swine-origin H1N1 influenza outbreak (36), although we also considered $R_0 = 1.2, 1.6, 1.8$, and 2.0. Age-specific death rates were based on estimates of excess pneumonia and influenza deaths from the 1957 and 1918 pandemics (fig. S2) (30, 31). We parametrized age-specific contact rates using data from a large-scale survey of daily contacts (28). These contact data show strong mixing between people of similar ages and moderately high mixing between children and people of their parents' ages (fig. S3).

We determined the optimal age-specific distribution of a limited number of vaccine doses for five different outcome measures. The first two were simply total infections averted and total deaths averted. We also used years of life lost, weighing deaths by the expected remaining years of life for

different ages. An additional measure was "contingent valuation" (10), derived from a survey of 3000 U.S. households (8) to give the disutility of deaths at each age. This measure resulted in a

valuation similar to "the investment refinement" principle (7), wherein young adults are most valued. Finally, for the outcome measure of economic cost, we included costs associated with

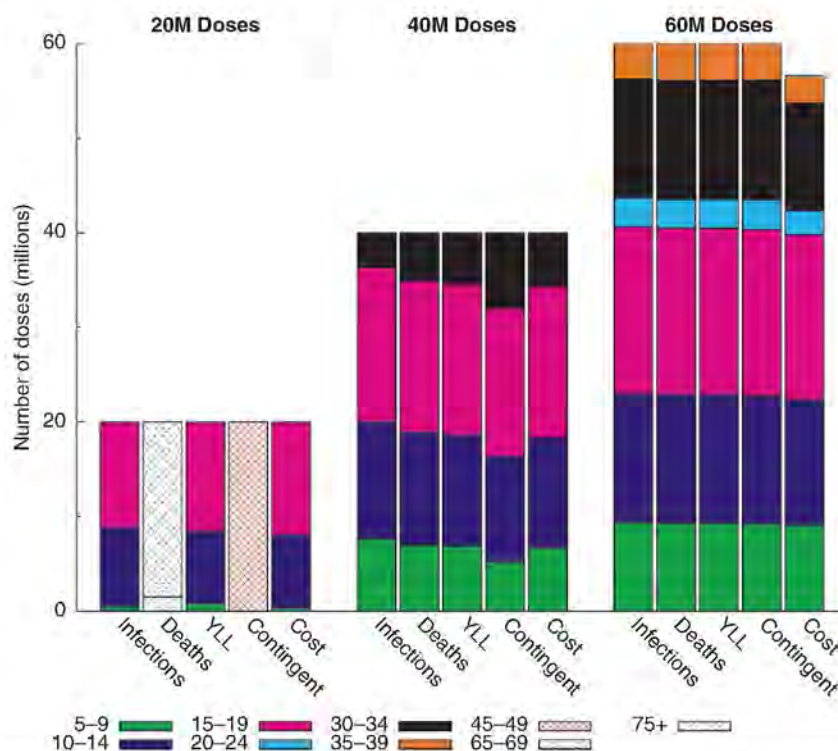


Fig. 2. Number of vaccines optimally distributed to each age group under the 1957 mortality pattern for 20 million, 40 million, and 60 million available vaccine doses, based on each outcome measure. Fewer than 60 million vaccine doses are used for the outcome measure of cost because the cost of vaccination (including side effects) is larger than its benefits when infection is unlikely because of herd immunity.

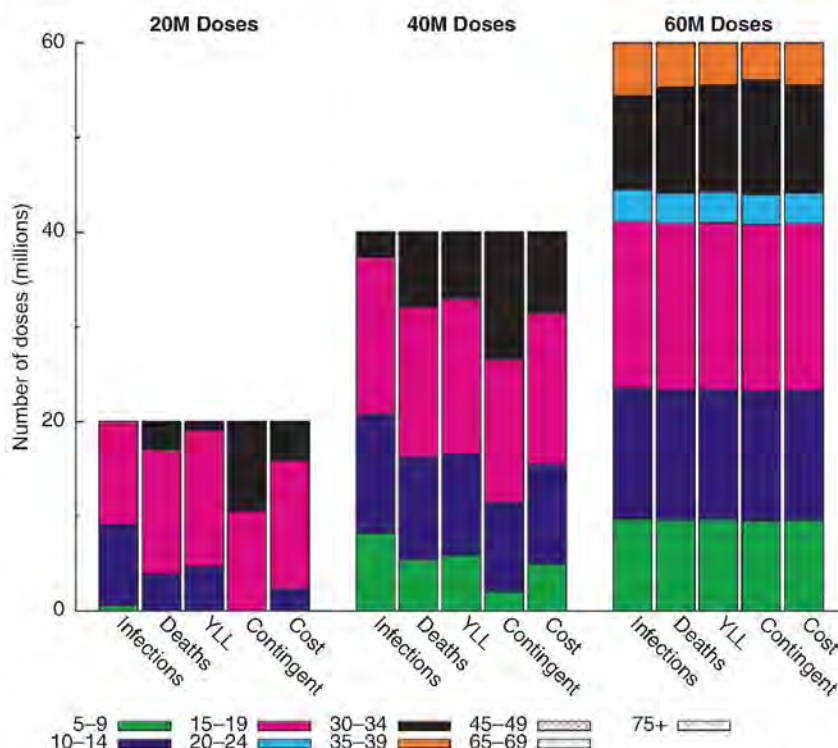


Fig. 3. Number of vaccines optimally distributed to each age group under the 1918 mortality pattern for 20 million, 40 million, and 60 million available vaccine doses, based on each outcome measure.

vaccination, as well as those associated with illness (table S2) (4, 34), and valued death using net present value of future lifetime earnings (9). Given that the value of future earnings is highest for young adults, this age group is most valued. The optimal vaccine distribution was then calculated using a numerical optimization routine for each outcome measure.

For our model influenza outbreak with $R_0 = 1.4$ and a mortality pattern similar to that in 1957, the optimal distribution of 63 million vaccine doses can extinguish the outbreak, whereas for the model influenza outbreak with a 1918 mortality pattern, 62 million vaccine doses can prevent the outbreak (fig. S14). Both of these totals are less than the 85 million vaccine doses that are currently administered annually for seasonal influenza. The optimal vaccine distribution in both cases is vaccination of people aged 5 to 19 and 30 to 39 (Fig. 1). Children 5 to 19 (37) are responsible for most transmission and for the spread of infection to their parents' age groups. Thus, both those most responsible for transmission and those they are

most likely to infect are prioritized, which in turn protects the remainder of the population. These results indicate that transmission must be explicitly considered when optimizing vaccine allocation.

To assess the effect of vaccine supply, we determined the optimal allocation of a range of available vaccine doses for both outbreaks (Figs. 2 and 3). When at least 37 million vaccine doses are available, all outcome measures prioritized vaccinating people aged 5 to 19 and 30 to 39 for the 1957 mortality pattern (Fig. 2 and fig. S7). Below 37 million vaccine doses, the outcome based on total deaths switched to prioritizing the elderly. Below 36 million vaccine doses, contingent valuation switched to prioritizing those aged 45 to 49 due to a combination of the economic productivity and greater infection severity of this age group. For the 1918 mortality pattern, all outcome measures were optimized by vaccinating people aged 5 to 19 and 30 to 39 (Fig. 3 and fig. S8).

Among the most fundamental characteristics of an influenza outbreak is its basic reproductive number, R_0 . The baseline scenario assumed $R_0 =$

1.4, chosen as an estimate for swine-origin H1N1 influenza (36). We also considered one less severe outbreak (with $R_0 = 1.2$) and three more severe outbreaks ($R_0 = 1.6, 1.8$, and 2.0) (27). When $R_0 = 1.2$, optimal vaccination only included ages 5 to 19 for all levels of vaccine availability and for both mortality patterns (figs. S16 and S17). For increased R_0 values, the outcome measure of infections averted continued to be optimized by allocation to children (ages 5 to 19) and added vaccination of adults 20 to 44 as more vaccine became available (figs. S18 to S23). Generally, for the outcome measures other than infections averted, as R_0 increased above, more vaccine doses were allocated to those at greatest risk of mortality. For 1957 mortality, older adults were added to some of the optimal allocations, first ages 65 and older, and then ages 45 to 64 for higher R_0 . Young adults 20 to 44 were added for higher R_0 for the 1918 mortality pattern. In addition, for 1918 mortality, it was never optimal to vaccinate adults 45 and older for any level of R_0 or vaccine availability. For all values of R_0 , when vaccine supply was plentiful, optimal allocation was vaccinating children and younger adults (20 to 44). The switch from protecting those at risk of mortality to those responsible for transmission occurred at higher levels of vaccine availability as R_0 increased. In all cases, deaths averted was the last outcome measure to switch to children and younger adults; other outcome measures switched markedly earlier in some cases.

The efficacy of the influenza vaccine varies from year to year. It is likely to be low for a zoonotic influenza strain, such as the currently circulating swine-origin influenza, and it is useful to be able to predict what might happen if vaccination strategies have reduced efficacy. Under these circumstances, we separated vaccine efficacy against infection and vaccine efficacy against mortality in our sensitivity analysis (27). For all outcome measures except infections averted, reducing vaccine efficacy against infection elevated prioritization of vaccinating those at greatest risk of mortality when vaccine supply was very limited (figs. S24 and S25). Reduced vaccine efficacy against death had a small effect on vaccine distribution when optimizing for any of the outcome measures (figs. S26 and S27). For novel influenza strains, older people may have acquired immunity from distant previous exposure. Such reduced susceptibility to the novel swine-origin H1N1 influenza may be present in the elderly (38). Incorporating this effect into our model resulted in the optimal vaccination no longer including the elderly for the one setting in which they were included in the baseline case: the 1957 mortality pattern with the outcome measure of deaths averted. Otherwise, the effect of reduced susceptibility on optimal vaccine allocation in the elderly was minimal (figs. S28 and S29). We also tested the impact of vaccination reducing the severity of infection by shortening the duration of infection and by decreasing infectiousness. Both shortened infection duration and reduced

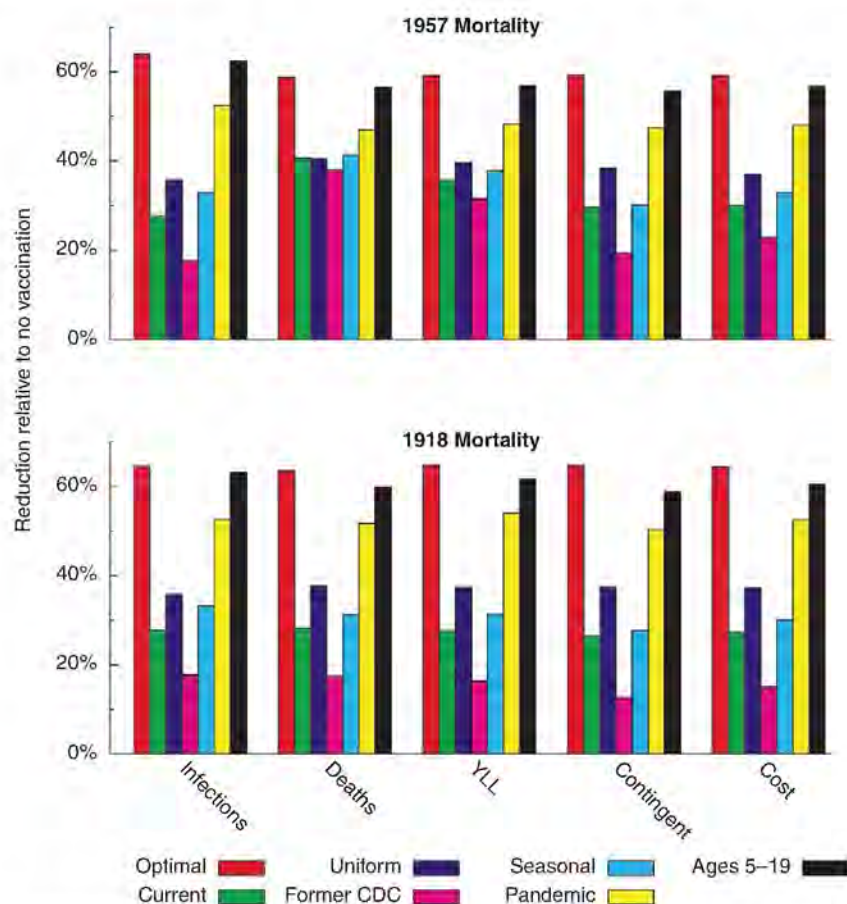


Fig. 4. Comparison of outcomes between optimal and alternative vaccination strategies for 40 million vaccine doses relative to a pandemic in an unvaccinated population for both 1957 (top) and 1918 (bottom) mortality patterns. We compare reductions in the five outcome measures resulting from the allocation of 40 million vaccine doses for seven different strategies: the strategy that optimizes the outcome measure (Optimal), the current levels of vaccination in the U.S. population (Current), uniform coverage of all age groups (Uniform), the former CDC age-based recommendations (Former CDC), the new CDC age-based recommendations for seasonal influenza (Seasonal), the new ACIP age-based recommendations for the novel swine-origin influenza (Pandemic), and uniform coverage of ages 5 to 19 (Ages 5–19). For each measure, the optimal distribution did markedly better than the strategies based on the CDC and ACIP recommendations.

infectiousness among vaccinees had little effect on optimal vaccine allocation (figs. S30 to S33).

Until the 2008 to 2009 influenza season, the U.S. Centers for Disease Control and Prevention (CDC) recommended for seasonal influenza the vaccination of children aged 6 months to 5 years old and of adults aged 50 and over. The CDC recommendations for seasonal influenza vaccination were expanded in 2008 to include children through age 18 (33). Recently, the CDC's Advisory Committee on Immunization Practices (ACIP) proposed guidelines for vaccinating against the novel swine-origin influenza that prioritize young people aged 6 months to 25 years (39), excluding the elderly due to their apparent reduced susceptibility (38).

We found that the previous as well as the new CDC policies for seasonal influenza performed substantially worse than our optimal strategies for all outcome measures (Fig. 4). For example, when at least 40 million vaccine doses are available for an outbreak with $R_0 = 1.4$, the entire population would be better protected by vaccinating schoolchildren (Figs. 2 and 3), who were not targeted by the previous CDC policy. In our model, the allocation of 40 million vaccine doses according to the previous CDC policy during an outbreak with the 1957 mortality pattern resulted in 102 million infections, 162,000 deaths, and a total cost of \$99 billion. The new CDC policy for seasonal influenza led to 83 million infections, 153,000 deaths, and \$86 billion in cost. The ACIP policy for swine-origin influenza resulted in 59 million infections, 139,000 deaths, and \$67 billion in cost. In contrast, the optimal strategies resulted in only 44 million infections, 108,000 deaths, and a total cost of \$53 billion. For the 1918 mortality pattern with 40 million vaccine doses, the previous CDC recommendations resulted in 102 million infections, 1.5 million deaths, and a total cost of \$1.7 trillion. The new CDC seasonal-influenza policy led to 83 million infections, 1.2 million deaths, and \$1.4 trillion in cost. The ACIP policy for swine-origin influenza produced 59 million infections, 853,000 deaths, and \$939 billion in cost. Our proposed optimal strategies resulted in 44 million infections, 645,000 deaths, and a cost of \$703 billion. The strategy of distributing vaccines uniformly to ages 5 to 19 also performed markedly better than the CDC and ACIP policies. Moreover, with the exception of the outcome measure of deaths averted when the mortality pattern is based on 1957, the CDC policies for seasonal influenza even performed worse than uniform allocation across all age groups, primarily as a result of the inefficient allocation of vaccine doses to the elderly and newborns. The CDC and ACIP's age-based recommendations could be substan-

tially improved by reducing the prioritization of the elderly and children under age 5, although the recent vaccination recommendations for swine-origin H1N1 show marked improvement over the recommendations for seasonal influenza.

For this particular comparison ($R_0 = 1.4$ with 40 million vaccine doses), the optimal allocations prevent substantial transmission, whereas the CDC and ACIP recommended policies do not, particularly those for seasonal influenza. For an outbreak with higher R_0 , when fewer vaccine doses are available, or when vaccine efficacy is low, the CDC and ACIP policies may be closer to optimal, depending on the outcome measure used. [The CDC and ACIP policies are likely closer to optimal for deaths averted (figs. S7, S18, S20, and S22.)] However, given the broad conditions under which vaccination of children and younger adults is optimal, such a policy is likely optimal except during severe vaccine shortages.

An age-structured mathematical model of influenza transmission has allowed us to determine the optimal allocations of vaccine doses for a variety of measures of population morbidity and mortality. Our results illustrate the importance of explicitly considering transmission when allocating vaccines, regardless of how vaccination outcomes are quantified. Our comparison with CDC and ACIP recommendations for both seasonal influenza and the novel swine-origin influenza suggest that CDC and ACIP recommendations are below optimum for all outcome measures, although recommendations for swine-origin H1N1 are a substantial improvement.

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UNIVERSITY OF Nebraska Medical Center

FACULTY POSITION IN BIOCHEMISTRY AND MOLECULAR BIOLOGY University of Nebraska Medical Center

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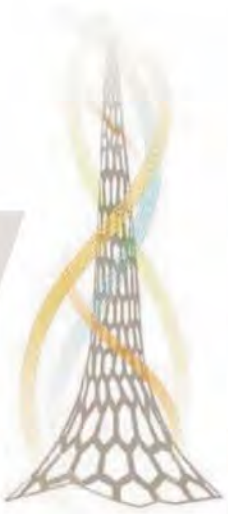
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Interested individuals should submit curriculum vitae, a one- to two-page summary of research interests and plans, and three letters of reference. Applications can be made electronically to e-mail: neurosearch@physiology.wisc.edu or they can be sent by mail to: Mary Walker, Faculty Search Committee 62653, University of Wisconsin School of Medicine and Public Health, Department of Physiology, 1300 University Avenue, Madison, WI 53706. To ensure consideration, please submit complete application by November 1, 2009. However, applications will be accepted until the position is filled.

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PUBLIC-PRIVATE PARTNERSHIPS: A RECIPE FOR SUCCESS?

The global financial crisis has beaten down science budgets everywhere. So it's no surprise that science-spending forecasts for Europe are grim. The EU's gross domestic product shrank by 2.5 percent this year. Consequently, politicians might cut science budgets to plug other shortfalls. In Italy, for example, Prime Minister Silvio Berlusconi's center-right government already has cut university budgets by 10 percent and has allowed them to fill only one in five vacant academic positions. Amidst the gloom over potential cutbacks, however, there are a few bright spots. **By Gunjan Sinha**

On the European Union level, science budget cuts are unlikely. The framework through which the EU funds research—Framework Programme 7 (FP7)—is dedicated money. Member states are legally committed to the €51 billion budget through 2013. Perhaps more important, FP7 initiatives that aim to stimulate economies are finally getting off the ground.

This spring the European Commission (EC) announced the first 15 research projects that will receive funding as part of the Innovative Medicines Initiative (IMI)—a unique public-private partnership that brings together large biopharmaceutical companies, small- and medium-sized enterprises, patient organizations, academia, hospitals, and public authorities to work through bottlenecks in developing new drugs.

IMI is one of six Joint Technology Initiatives (JTIs). Through this scheme, industry must at least match money offered by the EC in six predefined areas. A JTI focuses on one specific industrial area, aims to develop new precompetitive technologies, addresses a market failure, and is funded by a combination of private and public investment.

The other JTIs are: Aeronautics and Air Transport (or Clean Sky); Embedded Computing Systems; Nanoelectronics Technologies 2020; Global Monitoring for Environment and Security; and Hydrogen and Fuel Cells.

"This might really be an important change in the way that the EU funds research projects," says **Peter Tindemans**, a Euroscience spokesperson who runs a consulting company that issues advice on science policy. "JTIs are focusing on key areas that present problems for all EU countries, and they've created a new system whereby the players themselves are responsible for funding the science that needs to be done."

So great is the enthusiasm over JTIs that some member states have launched similar initiatives. In 2007, Spain set up the National Strategic Consortiums for Technological Research (CENIT) program that makes €750 million available to companies that at least match government funding. The same year, Germany launched a Pharmaceuticals Initiative which aims to distribute €800 million in public funds over *continued »*



“The Innovative Medicines Initiative aims to pool scientific expertise to create better methods and tools that streamline the drug development process.”

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"The more data you have, especially when it is generated by different groups, the more sure you can be of your results."

—Märta Sörgerdahl



five years through measures that aim to boost pharmaceutical and biotechnological research and development in Germany.

Through such measures, nations hope not only to boost their economies in the short term, but also to foster relationships that will ensure companies continue to invest within their borders in the future.

New Medicines Needed

Fostering long-term relationships is part of IMI's goal, too. Because rather than funding the development of new medicines, the IMI aims to pool scientific expertise to create better methods and tools that streamline the drug development process.

For example, among the first 15 projects selected for funding is one involving 12 academic institutions and 10 different companies that aims to find biological markers of chronic pain. Called EUROPAIN, the project will comprise six programs of research and has an estimated budget of at least €12.5 million through 2013. Two of the research programs will try to identify novel pain mediators and elucidate nervous system changes that contribute to pain. They will also refine ways to measure pain. Three programs will explore human pain mechanisms; one program will develop ways to integrate data from all five programs.

"The problem in pain management is that we are limited to very few classes of drugs," says Märta Sörgerdahl, medical science director at AstraZeneca—the company that is coordinating EUROPAIN. Pain medication is effective in less than one in every three patients, she adds, and while that ratio is good for many diseases, it isn't adequate for pain management because people suffer. "There is a great need for new drugs," she says.

And while many academic groups involved in the consortium have worked together and worked with industry before, this consortium offers the opportunity and the resources for academia and industry to work together to generate data more quickly. For example, industry and academia will jointly develop guidelines on how specific experiments should be done. These in turn can be used by all members in the consortium to conduct future research. "The more data you have, especially when it is

generated by different groups, the more sure you can be of your results," Sörgerdahl says. Each consortium member can then take any tools or technology developed by EUROPAIN and use it internally or with collaborators to develop proprietary drugs.

The US Comparison

IMI is similar to the US Food and Drug Administration's (FDA) Critical Path Initiative launched in 2004. However, they rely on different paths to improve drug development. FDA initiated Critical Path, but the program has no established structure nor does it have significant funding. By contrast, IMI aims to have its own governing body and will administer its own calls for funding—plus its budget is upward of €2 billion over five years.

Companies point to positive experiences with the Critical Path Initiative as proof that such collaboration can produce results. Responding to Critical Path, Novartis spearheaded three cooperative research projects in 2004, one of which was a precursor to an IMI project for which the company has also been selected to receive EU grant money. In one of those earlier efforts, in collaboration with Merck, Novartis focused on drug-induced kidney toxicity. The goal was to identify and validate biomarkers that can flag early insult to the kidney—before the organ's pathology has changed. Company scientists were also looking for markers that would specifically identify which part of the kidney was affected. Both companies had already identified nephrotoxicity biomarkers, but they needed to validate them. Ultimately both ran antibody-based assays on two different platforms to correlate and confirm each other's results.

The results were later folded into the Critical Path Initiative's Predictive Safety Testing Consortium, officially established in 2006, that enables member companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. Critical Path scientists acted as neutral arbiters so that other consortium members, which included 16 companies in total, could cross-validate Novartis's and Merck's results.

"It sounds pretty simple, but it was extremely complicated," says Jacky Vonderscher, former global head of biomarker development at Novartis. Vonderscher wasn't just referring to the science. Sorting out intellectual property and data sharing issues ate up a lot of time. At one point there were 35 lawyers sitting around a table to negotiate the consortium contract, Vonderscher recalled—and this was regarding research that wasn't yet competitive.

Organized to Avoid Bureaucracy

Indeed, such bureaucratic legal wrangling is one major gripe about JTIs. European scientists often complain about the amount of paperwork involved when working with EU grant money. But Sörgerdahl remains unconcerned. "Most of the major pharmaceutical companies are involved with EUROPAIN including GlaxoSmithKline, Pfizer, sanofi-aventis, and Eli Lilly and Company. These companies have in-house expertise that is accustomed to streamlining bureaucracy *continued »*

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Applications of NMR in solid materials



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Attn: Mag. Bettina Karnolz
Human Resources/Legal Advice
bettina.karnolz@ist.ac.at

For more information about IST Austria visit:
www.ist.ac.at

Focus on Europe

and organizing research," she says. "We all want to work efficiently," Sörgerdahl continues. "I'm confident this is going to work."

Certainly the projects funded by IMI won't be alone in this regard. But this is precisely why each JTI will have its own governing body, independent of the EC, say organizers. "My intent is to make it reactive, flexible, and involved," says Eric Dautriat, executive director of the Clean Sky Initiative. Dautriat is in the process of recruiting about 20 people who will comprise the Clean Sky Joint Undertaking—an entity that will manage the program. "There is no reason why we should be smothered by bureaucracy," he adds.

Clean Sky's mission is to develop environmentally friendly aircraft. Without a financial boost from the EU, green aircraft technologies would not develop quickly, says Dautriat, because there isn't enough market pressure right now. But Clean Sky gives companies a structure through which they can collaborate to develop mutually beneficial technologies.

So, for example, one project seeks to develop an open rotor—a propeller design that can potentially burn up to 30 percent less fuel compared to current engines as well as reduce

emissions and noise. Different companies are taking their own tack to achieve the same goal. Chichester, England-based Rolls Royce, and Snecma of Courcouronnes, France, are focusing on direct-drive turbofans with slightly different designs; in parallel Munich-based MTU Aero Engines in collaboration with Pratt & Whitney is preparing a demonstration of a geared turbofan. Each of these different solutions will be evaluated and compared with one another. All European companies involved in civil aviation are participating in Clean Sky and there are a total of 86 members, in addition to which hundreds of partners will be added through calls for research proposals.

"Clean Sky embraces all sectors of commercial aviation and combines the strengths of all stakeholders," says Dautriat. "This is already a significant achievement."

Spain On Board

JTIs have the potential to garner so much private investment that EU member countries have adopted similar programs to boost each nation's research productivity. For example, in 2007, Spain launched Ingenio 2010—a series of measures aimed to boost the nation's research and development spending from a low of 1.13 percent of gross domestic product to be more on par with the EU average of 1.77 percent.

One arm of the program, CENIT, offers grant money to research consortiums that in turn at least match the amount of government money. It makes €750 million in public money available over four years to research consortiums that aim to pursue projects in predefined areas including biomedical sciences, information technology, and renewable energies.

Similar to IMI, one project aims to design new methods to better predict toxicity of new molecular entities to speed up preclinical research. "The organizers noticed that they had the potential to tap our expertise on hepatic cells," explains Joan Guinovart, head of the project at Barcelona's Institute for Research in Biomedicine (IRB). The IRB is one of nine academic institutions collaborating on the project together with eight companies. Called MELIUS, the project was spearheaded by Madrid-based Noscira and is operating with a total budget of €20.5 million over five years.

The benefits of such collaboration flow both ways. "We have explored avenues that we otherwise would not have explored," says Guinovart. Working with molecules that inhibit specific pathways, for example, has revealed that they don't always exert an effect in predictable ways, he explains. "We have learned to be more cautious and keep an open mind." Moreover, the MELIUS project has fostered a relationship between Guinovart's research group and the companies involved; they are presently discussing collaborating on projects outside of MELIUS.

Germany Boosts Pharma R&D

It was with these same goals in mind that Germany launched the Pharmaceuticals Initiative in 2007. Unlike Spain, where pharmaceutical and biotechnology investment represent a small slice of the economy, Germany is home to the largest number of biotechnology companies in the EU. *continued »*

Featured Participants

AstraZeneca
www.astrazeneca.com

Clean Sky
www.cleansky.eu

European Commission
ec.europa.eu/index_en.htm

Euroscience
www.euroscience.org

German Federal Ministry of Education and Research
www.bmbf.de/en

Innovative Medicines Initiative
www.imi.europa.eu

Institute for Research in Biomedicine
www.irbbarcelona.org/index.php/en

Max Planck
www.mpg.de/english/portal/index.html

Merck
www.merck.com

National Strategic Consortiums for Technological Research
www.transport-research.info/web/programmes/programme_details.cfm?ID36682

Novartis
www.novartis.com

US Food and Drug Administration
www.fda.gov

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The Faculty of Health Sciences now aims to expand its research activities, and is seeking 4 new senior group leaders, as well as a number of Postdocs:

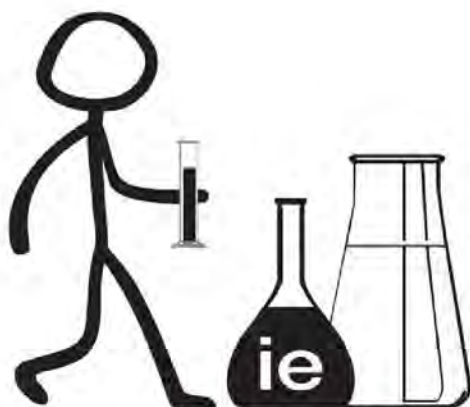
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Focus on Europe

“This might really be an important change in the way that the EU funds research projects.”
—Peter Tindemans



Yet hardly any therapeutics developed by biotech companies originate from Germany today, says **Benedikt Wolbeck**, a spokesperson for the German Federal Ministry of Education and Research (BMBF). The record for German pharmaceutical companies is almost as grim. Even though Germany is home to several such companies, a survey by the European Commission revealed that German pharmaceutical companies had developed only six of the 140 active substances licensed in 2005 in the EU. While German companies may carry out early research, most market innovations are generated in the USA, the UK, and Switzerland, Wolbeck adds.

To promote technology transfer at home, the Pharmaceuticals Initiative is dedicating over €800 million through 2011 to promote pharmaceutical and biotechnology research. Although the funds will finance both basic and application-oriented measures, the way in which the funds will be doled out is part of a new strategy to focus on strengthening the pipeline from research to market. And unlike JTIs or Spain's CENIT, matching funds from industry aren't a requirement. Rather, the BMBF has created other structures through which industry can contribute, such as investment funds.

One measure, called the BioPharma Competition, selected three projects out of 37 to receive a total of €100 million over five years, beginning this year. One winner is the Max Planck Drug Discovery & Development Center in Dortmund. The center will pool the most promising research on new compounds from all 12 Max Planck Institutes and come up with a strategy to further develop them. This includes technology licensing deals and handling decisions to conduct further research by taking compounds through phase IIa clinical trials to make them more attractive to industry. To finance the BioPharma projects, BMBF has created a fund that will be managed by London-based Inventive Capital Advisor, LLP. Companies will have the opportunity to invest in research by contributing to the fund or by contributing money to specific projects.

Another winner, the Neuroallianz consortium, consists of 12 partners that aim to bring research on new treatments and diagnostic tests for neurodegenerative diseases to the market. The third winner will focus on multiple sclerosis, specifically on moving basic research on therapies and diagnostic tools to market.

The BioPharma Competition is just one part of a package of measures. The remaining €700 million will be spent on various other measures to support clinical research, molecular diagnostics, and research on technology that can speed up drug development.

Through such initiatives, “we are unlikely to become *the* world's pharmacist in the long term,” said BMBF State Secretary Frieder Meyer-Krahmer during the BioPharma award ceremony in Berlin, “but we should at least be *one of* the world's pharmacists.”

Other Benefits

Certainly the idea to offer incentives to the private sector to invest within a nation's borders is a time-tested method to create jobs and grow economies. But such incentives often take the form of tax-breaks, reimbursement of capital expenditure, or other types of financial benefits. Offering public money to the private sector in ways that encourage development in specific areas represents a paradigm shift: profit and job growth are no longer the only end-points.

“As a publicly funded scientist I have a moral obligation to contribute to the industry of the country,” says Guinovart, who spends most of his time involved in basic research. But collaboration with industry gives him the opportunity to generate more concrete results. “I feel like I am returning something to society,” he says.

Moreover, the results of such focused research can potentially benefit everyone. “Each JTI is very specific,” comments **Catharine Ray**, spokesperson for science and research at the European Commission. “Each of them has an application in a strategic field and should allow a quicker commercialization of truly break-through technologies.”

At the EU level, public-private research collaborations are also supported by the Cooperation program, part of FP7. But many European scientists complain that project grants are often barely enough to cover costs. By contrast, JTIs leave open the possibility of higher investments from industry with fewer restrictions on how the funds should be spent. Industry partners in the EUROPAIN project, for example, are contributing €7.5 million to the budget as compared to the EC's €5 million, and are prepared to invest even more, says Sörgerdahl.

More important, adds Tindemans, JTIs should perhaps serve as a model for how to conduct public-private research collaborations in the future. “The EC should really move away from funding all of these small projects [supported under Cooperation],” says Tindemans. JTIs enable very large projects with all the major players involved. “This should be a focus of even more EU funding.”

Gunjan Sinha is a freelance writer living in Berlin, Germany.

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Edgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Professor of Nanoscale Multifunctional Ferroic Materials and Devices

The Department of Materials Science of ETH Zurich (www.matl.ethz.ch) invites applications for a professorship of Nanoscale Multifunctional Ferroic Materials and Devices.

Activities from basic research to devices including potential new applications are anticipated.

It is expected that close, collaborative relationships with other department members, both theoretical and experimental, in all materials classes will be established. The professor will be expected to teach students in Materials Science at all levels, as well as holding special courses for other disciplines (i.e. physics, electrical engineering, chemistry). He or she will be expected to teach undergraduate level courses (German or English) and graduate level courses (English).

The successful candidate with strong physical and chemical background has several years of experience in the fields of structure-processing relations of ferroic materials, ferromagnetic properties or with transport phenomena in highly correlated systems, non-trivial size effects in complex inorganic materials and heterostructures.

Please submit your application together with a curriculum vitae and a list of publications to the President of ETH Zurich, Prof. Dr. Ralph Eichler, Raemistrasse 101, 8092 Zurich, Switzerland, no later than November 30, 2009. With a view towards increasing the proportion of female professors, ETH Zurich specifically encourages female candidates to apply.

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Postdoc in Lymphatic Endothelial Biology in Switzerland

The Laboratory of Lymphatic Bioengineering, an interdisciplinary and dynamic lab that is part of the Bioengineering Institute within the School of Life Sciences at the EPFL, is seeking applications for a postdoctoral fellow to study the role of lymphatic vessels in lipid metabolism. The ideal applicant will have a PhD in vascular biology or bioengineering or a related field, and experience with animals and in vivo imaging or microscopy; he/she should be highly motivated, independent, and have excellent writing skills. Interested candidates should send a CV with three references to Melody Swartz at melody.swartz@epfl.ch.

For more information on the lab or the EPFL please visit our websites:
Swartz lab: <http://lmbm.epfl.ch>
Bioengineering: <http://ibi.epfl.ch>
Life Sciences: <http://sv.epfl.ch>



TWO FACULTY POSITIONS Biological Sciences

The Department of Biological Sciences at the University of Pittsburgh invites applications for two full-time tenure-track faculty appointments (**Ecology and Evolution; Biological/Biomedical Sciences**), pending budgetary approval. Appointments are anticipated to begin in September 2010 and will continue to advance our goal of establishing a broad-based interactive community of scientific researchers in modern biology. We encourage candidates working in any area of biological sciences to apply; we especially encourage applications from those working in the following areas:

I. Ecology and Evolution

- Community, Ecosystem or Global Change ecology
- Theoretical ecology or evolution
- Genomic, Phylogenetic, Molecular or Developmental evolution
- Animal, Plant or Microbial systems

II. Biological or Biomedical Sciences

- Microbiology, including host-pathogen interactions
- Systems biology
- Cell and Developmental Biology, including neurobiology and physiology
- RNA biology
- Macromolecular Structure/Function

We anticipate making both appointments at the **ASSISTANT PROFESSOR** level. The successful candidates must have a Ph.D. and extensive postdoctoral experience and will be expected to establish extramurally funded research programs, train graduate students, and actively participate in undergraduate education and research. To ensure full consideration, applications should be received by **November 1, 2009**. Applicants should email a single PDF document identifying the search they would like to be considered for in the subject line and containing a curriculum vitae, a statement of research accomplishments and goals, and a brief description of teaching interests to biojobs@pitt.edu. In addition, applicants should arrange to have at least three letters of reference sent to:

Search Committee
Department of Biological Sciences
University of Pittsburgh
Pittsburgh, PA 15260
(412) 624-4266

Further information on the Department of Biological Sciences is available at:
<http://www.pitt.edu/~biology>

The University of Pittsburgh is an Affirmative Action, Equal Opportunity Employer. Women and members of minority groups under-represented in academia are especially encouraged to apply.



**Call for Applications and Nominations
For the
POSITION OF DEAN
School of Solar and Advanced Renewable Energy
(SSARE)**

The University of Toledo (UT) invites nominations and applications for the position, Dean of the School of Solar and Advanced Renewable Energy (SSARE) at UT. This position is a full time appointment available immediately; however, timing can be adjusted to the needs of the successful candidate.

The University of Toledo was established in 1872. Today it is the third largest of 13 public universities in Ohio. It is a diverse, student centered, metropolitan research university distinguished by its exceptional strength in science and technology and its effective, transformational leadership. It is widely respected and highly acclaimed for its world class initiatives in teaching, research, incubation, and commercialization in the fields of Solar and Advanced Renewable Energy. A particular point of pride at UT is its distinguished cadre of teaching and research faculty and its state and federally funded research in second and third generation photovoltaic (PV) materials. Biofuels, energy storage, and wind technologies research are also priority programs.

The University of Toledo's commitment to building on its strength in energy is evidenced by the recent establishment of the School of Solar and Advanced Renewable Energy (SSARE) at UT by the President and the Board of Trustees. This School is a model for UT's strong intercollegiate relationships and has the full endorsement and support of the Deans of the Colleges of Arts and Sciences, Engineering, Business, and Graduate Studies.

The successful candidate for Dean of the School of Solar and Advanced Renewable Energy (SSARE) must be a respected, recognized leader with a demonstrated record of administrative achievement in academia, business, and/or public service. He/she will be recognized for scholarship; have a commitment to institutional excellence, a passion for transformative change and for innovation, and the credentials and interpersonal skills to recruit and retain the best and the brightest faculty, researchers, and students to the SSARE at the University of Toledo.

This position offers a unique opportunity to implement and grow a results oriented entity in a field of acknowledged regional, national, and global need. Graduate and undergraduate degrees will be offered initially through the partnering Colleges but are planned to quickly become part of SSARE's portfolio. Research will be a hallmark of SSARE, funded by existing and new grants and awards, and provide a continuum for the notable UT successes to date in solar and advanced renewable energy (SARE). Outcomes will include spin off incubator initiatives leading to full commercialization and significant economic development consistent with the UT goal of "transforming northwest Ohio into a place of innovations."

UT's commitment to the planned early success of SSARE is further evidenced by the current installation of a 10-kilowatt thin film solar array on the grounds and on the rooftops of the UT Scott Park Campus of Energy and Innovation, in tandem with wind and other advanced renewable energy technologies.

Salary will be negotiable commensurate with experience. UT also offers a generous benefits package. Letters of nomination and applications from qualified, interested candidates (a letter, complete CV and contact information for at least three professional references) should be submitted electronically to:

Dr. John Gaboury
Vice Provost and Chair,
SSARE Dean Search Committee
University of Toledo
c/o john.gaboury@utoledo.edu
419-530-2738

Consideration of applications will begin after **October 23, 2009**, and will continue until the position is filled.

*The University of Toledo is an Equal Access, Equal Opportunity,
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**Tenure Track Faculty Positions
in Stem Cell Biology**

Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center invites applications for junior tenure-track faculty positions in the Program in Developmental Biology. Individuals studying embryonic stem cells, adult stem cells, iPS cells or regulation of pluripotency in any animal will be considered for the position. SKI is located in a rich environment for stem cell studies (http://www.triscistemcell.org/about_us.html) and New York State is committed to the support of stem cell research (<http://stemcell.ny.gov/>). The Developmental Biology Program offers a highly interactive and exciting research environment, with expertise in stem cell biology as well as mouse, *Drosophila*, and *C. elegans* development. Sloan-Kettering Institute offers outstanding infrastructure and resources to support research (<http://www.ski.edu>). New faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program.

Candidates should e-mail their application in PDF format to devbio@mskcc.org by November 1, 2009. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three letters of reference on letterhead sent in PDF format by e-mail to devbio@mskcc.org. The letters should arrive by November 1, 2009. Inquiries may be sent to **Ms. Lennon** or to **Dr. Kathryn Anderson**, Chair, Developmental Biology Program, Sloan-Kettering Institute at devbio@mskcc.org. Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer/AA. Smoke-free environment.



Memorial Sloan-Kettering
Cancer Center
www.mskcc.org

**Faculty Position
Structural Biology Program
Sloan-Kettering Institute**

The Structural Biology Program of the Sloan-Kettering Institute (www.ski.edu) invites applications for a tenure-track faculty position at the Assistant Member level (equivalent to Assistant Professor). We are interested in outstanding individuals who have demonstrated records of significant accomplishment. Areas of interest include x-ray crystallography, NMR spectroscopy, EM and optical imaging, as well as the interface of structural, chemical and computational biology. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

Candidates should e-mail their application in PDF format to structbio@mskcc.org by December 1, 2009. The application should include a CV, description of past and proposed research (3-7 pp), and copies of three representative publications. Candidates should arrange to have three signed letters of reference in PDF format sent by e-mail to structbio@mskcc.org. The letters should be addressed to **Dr. Nikola Pavletich**, c/o Julie Kwan, Box 135, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065. Inquiries may be sent to **Ms. Kwan** or to **Dr. Nikola Pavletich**, Chair, Structural Biology Program at structbio@mskcc.org. Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer. Smoke-free environment.



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NIH Intramural Research Program is Recruiting “Earl Stadtman Investigators”



The National Institutes of Health, the nation's premier agency for biomedical and behavioral research, is pleased to announce the launch of its search for top-tier tenure-track candidates to become “NIH Earl Stadtman Investigators.”

Earl Stadtman was an outstanding NIH scientist who mentored many current leaders in the biomedical community. In his honor, the NIH is recruiting basic, clinical and population-based investigators who seek the flexibility of scientific exploration in an intellectual and supportive environment. NIH investigators have the ability to focus on research that is high risk; they can quickly redeploy resources to explore new directions, collaborate freely on multidisciplinary teams, and contribute to the NIH mission of improving human health. The receipt of prestigious awards and honors—Nobel prizes, Lasker awards, elections to the NAS and IOM, among others—demonstrates the scientific rigor of our NIH intramural investigators.

We offer competitive startup packages and a collaborative, academic environment with more than 1,100 principal investigators engaged in cutting-edge basic, translational, clinical and population-based research. Our scientists focus entirely on their research with ample opportunities to mentor and train outstanding fellows at all levels. One special feature of our research program is the NIH Clinical Center, the world's largest hospital entirely devoted to biomedical research.

Qualifications/Eligibility: Candidates must have an M.D., Ph.D., D.D.S./D.M.D., D.V.M, D.O. or equivalent doctoral degree and have an outstanding record of research accomplishments as evidenced by publications in major peer-reviewed journals. Preference will be given to applicants who are in the early stages of their research careers. Candidates in any area of biomedical, clinical and behavioral research are invited to apply. Appointees may be U.S. citizens, resident aliens or non-resident aliens with, or eligible to obtain, a valid employment-authorized visa.

Salary: Successful candidates are offered competitive salaries commensurate with experience and qualifications, and they are assigned ample research space, supported positions and an operating budget.

To Apply: Complete applications should be received by November 1, 2009; however, applications will be accepted until available positions are filled. Interested applicants should submit a curriculum vitae, a three-page description of proposed research, and three letters of recommendation through our online application system, at <http://tenuretrack.nih.gov>. No paper applications will be accepted.

For information on the NIH Intramural Research Program, refer to <http://intramural.nih.gov/search> and <http://www1.od.nih.gov/oir/sourcebook/sci-prgms/sci-prgms-toc.htm>. Specific questions regarding this recruitment effort may be directed to Dr. Roland Owens, Assistant Director, NIH Office of Intramural Research at owensrol@mail.nih.gov.

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Positions @ NIH

THE NATIONAL INSTITUTES OF HEALTH



STAFF SCIENTIST

The National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH) performs research in computational biology and creates and maintains information systems and computational tools for the biological research community. The Computational Biology Branch is seeking a Staff Scientist to lead the development of computational approaches for the analysis of high-throughput sequencing, genotyping, and clinical data.

The NCBI is looking for an outstanding candidate to work on the multi-source data being produced by the National Heart, Lung, and Blood Institute's (NHLBI) Systems Approach to Biomarker Research in Cardiovascular Disease (SABRe CVD) Initiative in Framingham Heart Study (FHS). This is a collaborative initiative between NCBI and the NHLBI to establish a joint program with genetic, genomic, proteomic, metabolomic, clinical, and computational components to characterize molecular signatures of CVD and its risk factors. The FHS resource includes thousands of genotyped individuals who have been studied for up to 60 years, and we are currently accumulating unprecedented amounts of gene expression, and 'omic' data to perform integrated analyses across multiple platforms in relation to disease phenotypes. The responsibilities of the Staff Scientist will include partaking in establishing a research program and facilitating interactions between research and data management groups at NCBI and NHLBI.

We are looking for an individual with a track record of outstanding research in population genetics, high-throughput sequencing, comparative genomics, and/or computational biology. Candidates may be U.S. or non-U.S. citizens and must have a Ph.D., strong publication record, and postdoctoral experience. The successful candidate will have excellent communicating skills and proven ability to successfully engage into a multi-disciplinary collaborative research. Successful candidates will serve on a non-competitive appointment in the excepted service. Salary and benefits are competitive, commensurate with education and experience. Interested individuals should send a copy of their CV, cover letter detailing research interests, and names of three references to [Ivan Ovcharenko at ovchare@ncbi.nlm.nih.gov](mailto:Ivan.Ovcharenko@ncbi.nlm.nih.gov).



Staff Scientist Position Laboratory of Cellular and Molecular Biology

The Laboratory of Cellular and Molecular Biology (LCMB), is seeking a Staff Scientist to lead a group investigating the transcriptional control of the chemokine RANTES.

The successful candidate must have an excellent understanding of transcriptional regulation and expertise with a variety of molecular techniques including microarrays, ChIP and ChIP/seq, siRNA knockdown, gene expression, and assay development for chemical library screening. Candidates must have a Ph.D. and/or M.D. degree with a minimum of four years of postdoctoral experience and a strong publication record in molecular biology. The NCI offers competitive salary commensurate with research experience and accomplishments. The incumbent will be eligible for a full civil service benefits package including: retirement, health insurance, life insurance, and participation in the Thrift Savings Plan (TSP). This position is located on the NIH campus in Bethesda, Maryland.

Interested applicants should submit a cover letter, curriculum vitae, a brief statement of research experience and interests, and request three letters of reference to be sent to:

Alan M. Krensky, M.D., Senior Investigator, Center for Cancer Research, NCI, LCMB, Building 37, Room 2016, 37 Convent Drive, Bethesda, MD 20892, Krenskya@mail.nih.gov.

POSTDOCTORAL POSITIONS

Department of Health and Human Services
National Institutes of Health

National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive
and Kidney Diseases

Postdoctoral positions are available in two collaborating laboratories investigating the developmental and/or cellular consequences of post-translational modifications of proteins. Recent studies suggest that certain protein modifications, such as glycosylation, are required for normal development and play roles in modulating cell signaling and integrin-mediated cell interactions. Future work will focus on a systems approach, using genetic, biochemical, cell biological and proteomic techniques, to determine how glycosylation regulates cell interactions during development. Candidates must have a Ph.D. or equivalent degree, a background in molecular biology/biochemistry and less than three years postdoctoral experience. Please send curriculum vitae, statement of interest, and contact information for three references to: Dr. Kelly Ten Hagen (Kelly.Tenhagen@nih.gov) and Dr. Lawrence Tabak (Lawrence.Tabak@nih.gov).



NIDDK NATIONAL INSTITUTE OF
DIABETES AND DIGESTIVE
AND KIDNEY DISEASES



Tenure-track Investigator Positions in Human Genetics and Developmental Neurobiology

Neurobiology-Neurodegeneration & Repair Laboratory

The Neurobiology-Neurodegeneration & Repair Laboratory (N-NRL) aims to facilitate translational research for treatment of retinal diseases by delineating fundamental mechanisms in development, aging and disease pathogenesis (www.nei.nih.gov/intramural/nnrl.asp).

We are seeking outstanding scientists who can establish innovative research programs in human genetics or developmental neurobiology with a focus on retinal biology and/or disease. Stem cell biology, synaptogenesis, statistical genetics and systems/network-based approaches are of special program relevance. Scientists with excellent training in diverse disciplines of biology and medicine are especially encouraged to apply. The candidates should have M.D. and/or Ph.D. degrees with training, experience and significant publication records in any of the relevant fields. No previous research in vision is required; however, applicants are expected to discuss future plans relevant to vision and/or blindness.

Salary is commensurate with research experience and accomplishments. A full Federal package of benefits is available (including retirement, health, life and long term care insurance, etc.)

Applications will be considered as they are received. The search will continue until suitable candidates are recruited. Interested individuals should send by email: a cover letter, curriculum vitae, a brief summary of research accomplishments and future goals, three significant publications, and letters from three references to:

**NEI-NNRL Tenure Track Search Committee
National Eye Institute, NIH**

**NEITTSC@nei.nih.gov
Fax: 301-480-1769**



WWW.NIH.GOV



NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

PROGRAM DIRECTORS, NEURODEGENERATION

The National Institute of Neurological Disorders and Stroke (NINDS), a major component of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS), is seeking applications from exceptional, visionary candidates with distinguished records in basic, translational and/or clinical neuroscience research to serve as Program Directors for the planning, evaluation, and administration of research on neurodegenerative disorders including Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD). This is an exceptional opportunity for two candidates to join a highly interactive group of scientists and clinicians at the NINDS who are working across all areas of neuroscience and on a wide range of neurological disorders.

Successful candidates will be accomplished neuroscientists who have a strong commitment to the advancement of basic, translational and clinical research, a demonstrated record of research program management, and outstanding leadership skills. As Program Directors, they will conceive, develop, and oversee cutting edge research programs in Neurodegeneration. Experience in basic neuroscience (genetic, molecular, cellular, circuit or systems level), translational neuroscience (therapy or diagnostic development) and/or clinical research is highly desirable. Applicants must have the capacity to interact effectively with national and international organizations and individuals who represent wide-ranging views and competing priorities. Additional criteria for selection will include: experience and skill in communicating scientific, programmatic, and policy information to lay and scientific audiences; skill in administrative and program management; a strong publication record in the field of neurodegeneration, especially AD, ALS and FTD; demonstrated success in establishing and maintaining collaborations with individuals inside and outside of the organization; and experience in organizing cross-agency or cross-institution projects. Familiarity with NIH grant-related policies and procedures is helpful but not required.

Applicants must possess a Ph.D. and/or M.D. degree, have experience in research program oversight, and demonstrate extensive involvement in independent and collaborative projects in the field of neurodegeneration. Applications may be submitted beginning 09/08/2009 to 12/01/2009. Application instructions can be found at the USAJobs Web Site (<http://www.usajobs.gov/>), by searching on Vacancy Announcement for Health Scientist Administrator GS-0601-13/14: NINDS-09-366942-CR-DE, NINDS-09-366942-MP or Medical Officer, GS-0602-13/14/15: NINDS-09-366806-DH. Applicants must be U.S. citizens. The salary ranges from \$86,927 to \$153,200 per annum and is commensurate with experience and qualifications. Full Federal benefits are available including leave, health and life insurance, long-term care insurance, retirement, and retirement savings plan (401k equivalent). For information concerning the nature of the job, please contact Dr. Emmeline Edwards (edwardse@mail.nih.gov).



National Institutes of Health (NIH), National Eye Institute (NEI) Chief, Laboratory of Computational Medicine

The NEI seeks to develop a new program in computational analysis that fully employs human genomic, transcriptomic, proteomic, metabolomic, neurophysiological and clinical data sets to reconstruct biological networks characteristic of normal and disease states. The magnitude, diversity, rich information content, and hierarchical connectivity of these data sets require the utilization and development of novel quantitative tools. The goal is to understand human disease at a molecular level in order to develop mechanism-based therapeutic interventions.

We invite applications for head of a new laboratory of Computational Medicine within the NEI Intramural Research Program. This initiative seeks to integrate and translate knowledge from genetics and biology to a wide range of disease processes using systems, network, statistical and bioinformatics approaches.

- Examples in ocular biology amenable to a systems approach would include neuro-immune interactions, gene regulatory networks during disease pathogenesis, protein interaction pathways, neuron-glial-vascular biological networks in the retina, neuronal networks in the CNS, and developmental conditions and disorders.
- The research program has interest in developing novel computational methodologies for analyzing large genetic, biological, biomedical, neuronal, and functional data sets. Particular attention will be paid to genotype-phenotype correlations, gene-gene and gene-environment interactions. In parallel, we will actively seek to develop disease intermediate phenotypes that reflect the underlying biology and pathophysiology of disease.
- Data sets from large clinical trials, genetic studies (including GWAS), expression profiling in normal and disease conditions, and from the eyeGENE human research repository for monogenic ophthalmic diseases will be developed to reconstruct and understand ocular biological networks that link genetic perturbations, small molecule interactions, and physiological processes, to predict normal and disease states

The NEI/NIH provides an exceptional environment of dedicated scientists as well as a wide range of resources. We currently envision that this program will be located in the newly constructed Porter Neuroscience complex that houses a diverse set of investigators from many different Institutes. The successful candidate will be expected to recruit tenure-track faculty in areas that may include computational medicine or neuroscience, network biology, genetic or molecular epidemiology, cell and molecular biology, statistical genetics, bioinformatics, and biostatistics into the new Laboratory of Computational Medicine. Applicants should have a MD, MD/PhD or PhD and an outstanding record of accomplishments in genetics, epidemiology, neuroscience, cell and molecular biology, biostatistics, or a related quantitative discipline. Senior scientists would have the opportunity to maintain their participation in existing collaborative research in non-eye diseases if desired.

This position will remain open until filled. Applicants should submit curriculum vitae, bibliography, copies of their five most significant publications, a summary of research accomplishments, names of three references, and a detailed experimental plan for the development of this program. These materials should be sent to: **The Office of the Scientific Director, National Eye Institute, Attention: Ms. Mica Gordon (gordonmi@nei.nih.gov), NIH Building 31, 31 Center Drive, Room 6A22, Bethesda, MD, 20892.**

Positions @ NIH

THE NATIONAL INSTITUTES OF HEALTH



DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH (NIH)
National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM), a component of the National Institutes of Health (NIH), Department of Health and Human Services, seeks an accomplished, innovative neuroscientist to serve as Scientific Director of its Intramural Research Program (IRP) and as senior investigator responsible for developing a new research program in mind-body medicine. This individual reports to the Director, NCCAM, and will serve as a member of the NCCAM leadership team.

As Scientific Director, you will articulate and implement a vision and oversee research infrastructure for highly unified and mutually supportive laboratory and clinical programs in the conduct of bench-to-bedside and bedside-to-bench research related to complementary and alternative medicine (CAM) therapies.

As Senior Investigator, you will have substantial committed resources to create a cutting-edge program of clinically oriented laboratory research and/or clinical studies that exploit the best current methods from the neuroscience disciplines to define the nature, mechanisms of action, safety, and efficacy of the CAM modalities that affect actions and interactions linking mind, body, and behavior.

This exceptional opportunity is available to an accomplished neuroscientist who has a demonstrated record of senior-level management of a large, nationally recognized research program, a commitment to both basic and clinical research, and leadership skills to forge team efforts with colleagues within intramural programs across the NIH.

Applicants must possess an M.D., Ph.D., or equivalent degree in a biomedical field related to the mission of NCCAM and have professional experience reflecting a broad scientific background and experience in basic and/or clinical investigation. Applicants must be able to interact with full authority; have the demonstrated capability to plan and direct research programs of national and international importance; and have the ability to communicate with and obtain the cooperation of national and international organizations and individuals who represent wide-ranging views and competing priorities. Salary is commensurate with qualifications and experience. Full Federal benefits including leave, health and life insurance, long-term care insurance, retirement, and a savings plan (401k equivalent). Qualified individuals are encouraged to email their CV, bibliography, list of three references, and cover letter outlining their relevant experience and vision for leading the NCCAM IRP to: nccamsrrecruits@mail.nih.gov, Subject Line: Scientific Director Search, Application Deadline: October 31, 2009, Email receipt of applications and inquiries is preferred; however, candidates needing reasonable accommodation may fax application materials to 301-402-4741.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
OFFICE OF THE DIRECTOR
ASSOCIATE DIRECTOR FOR LEGISLATIVE POLICY AND ANALYSIS



The Office of the Director (OD) of the National Institutes of Health (NIH) in Bethesda, Maryland, invites applications for the position of Associate Director for Legislative Policy and Analysis. This is a career Federal position in the Senior Executive Service. The Associate Director for Legislative Policy and Analysis provides executive leadership and direction for NIH legislative policy, analysis, development, strategy, and liaison relevant to NIH programs and activities. As the senior legislative official for NIH, the incumbent analyzes the overall legislative needs of the NIH, directs the development of legislative proposals and testimony, and provides liaison with congressional committees. Other responsibilities include: advising the Director, NIH, and senior staff on political issues and on pending legislative and oversight activities; representing the agency on legislative matters, as appropriate; and managing legislative policy and liaison activities with the Congress, the Department, and other agencies regarding pending legislation that may affect NIH and the national medical and health related research community. This position is also responsible for implementation of law, including appropriations. The incumbent manages the Office of Legislative Policy and Analysis and reports to the Director, NIH. A full package of Civil Service benefits is available including retirement, health and life insurance, long-term care insurance, leave, and a 401k equivalent savings plan. A detailed vacancy announcement, along with mandatory qualifications and application procedures, can be obtained via the NIH Home Page at: <http://www.jobs.nih.gov> under the Executive Jobs section (Announcement Number: OD-09-05SES) or by contacting Lynrita Jacobs at seniorre@od.nih.gov or calling 301-402-4077. Applications must be received electronically by 11:59 p.m. on Monday, September 21, 2009.



WWW.NIH.GOV

Clinical Tenure Track Position

The National Institute of Allergy & Infectious Diseases (NIAID), Division of Intramural Research (DIR), is seeking an outstanding tenure-track investigator to develop a clinical research program to better understand, treat, and ultimately prevent infectious, immunologic, and/or allergic diseases. The successful candidate will implement and direct an independent clinical research program with an emphasis on clinical studies but which may include translational and basic research. The incumbent can choose the laboratory with which he or she would prefer to be affiliated. Any clinical protocols developed should complement the research goals of the selected laboratory. In addition, the incumbent will be paired with a senior investigator, who will serve as a clinical mentor.

An outstanding postdoctoral record of research accomplishment and an M.D., M.D./Ph.D., or equivalent degree is required for this position; board eligibility/board certification is also required. The incumbent will be expected to meet the requirements for authorization of patient care privileges by the Credentialing Services of the NIH Clinical Center.

Candidates will be assigned independent resources to include clinical and/or laboratory support personnel, equipment, space, and an allocated annual budget for services, supplies, and salaries sufficient to foster success. This is a tenure-track appointment under Title 42. Salary is dependent on experience and qualifications.

Interested candidates may contact

Dr. Karyl Barron, DIR deputy director at 301-496-3006 or kbarron@nih.gov for additional information about the position.

To apply for the position e-mail your curriculum vitae, bibliography, and an outline of your proposed research program (no more than two pages), by November 3, 2009 to Ms. Yushekia Hill at NIAID.DIR.Search@niaid.nih.gov. In addition, send three letters of recommendation to Chair, NIAID DIR Clinical Tenure Track Search Committee, c/o Ms. Yushekia Hill at NIAID.DIR.Search@niaid.nih.gov or 10 Center Drive MSC 1356, Building 10, Room. 4A-22, Bethesda, MD 20892-1356. E-mail is preferred. Please note search #027 when sending materials.



NIAID

National Institute of Allergy and Infectious Diseases

Further information about
DIR laboratories is available at:
www.niaid.nih.gov/about/organization/dir/default.htm
and information on working at NIAID
is available on our website at
www.niaid.nih.gov/careers/sdtt.



US DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



National Institute of Allergy and Infectious Diseases
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Positions @ NIH

THE NATIONAL INSTITUTES OF HEALTH

Chief, Laboratory of Infectious Diseases

The **National Institute of Allergy and Infectious Diseases (NIAID) Division of Intramural Research (DIR)** seeks an outstanding individual to head the **Laboratory of Infectious Diseases (LID)** located in the main NIH campus, Bethesda, MD. A DIR laboratory chief is equivalent to a department chair in a university or medical school. LID has a long and successful history of development of antiviral vaccines and in the study of immune responses to viruses; the pathogenesis of viral infections; the molecular biology, antigenic diversity, and genetics of viruses; and, with the application of epidemiologic principles, the discovery of viral agents that cause previously unrecognized diseases or diseases whose cause was not previously established. The laboratory maintains a broad, flexible, and diverse scientific environment that supports and stimulates the activities of the vaccine programs at NIAID, including rapid development and testing of vaccines and immunoprophylactic agents in both developed and developing countries.

This position requires an individual with a Ph.D., M.D., D.V.M., or equivalent degree with proven ability to carry out a strong independent research program. Preference will be given to candidates with a record of leadership and accomplishment in vaccine discovery and development as well as in the study of viral pathogenesis. The selected individual will also be expected to recruit other principal investigators with independent research programs, manage a complex organization, lead a vaccine production unit, and oversee clinical trials in the United States and abroad. In addition, she/he will be expected to conduct an independent laboratory and/or a translational/clinical research program. Salary is dependent on experience and qualifications.

Generous ongoing support for salary, technical personnel, postdoctoral fellows, equipment, and research supplies will be provided. Available cores or collaborative facilities include flow cytometry, advanced optical imaging, microarray generation and analysis, high throughput sequencing, computational biology, production of transgenic and gene-manipulated mice, biosafety level 3 facilities, chemical genomics, and support for projects involving RNAi screening. In addition to an outstanding international postdoctoral community, a superior pool of graduate and undergraduate students is available to the successful applicant.

Interested candidates may contact DIR Director Dr. Kathryn Zoon at 301-496-3006 or kzoon@niaid.nih.gov for additional information about the position.



NIAID

National Institute of Allergy and Infectious Diseases

To apply, submit your curriculum vitae, bibliography, and a detailed statement of how your expertise can contribute to the success of the LID to Yushekia Hill at NIAID_DIR_Search@niaid.nih.gov. In addition, three letters of reference must be sent directly from the referee to Dr. John Gallin, Chair, NIAID Search Committee, c/o Yushekia Hill at NIAID_DIR_Search@niaid.nih.gov or 10 Center Drive, MSC 1356, Building 10, Room 4A22, Bethesda, MD 20892-1356. E-mail is preferred. Applications will be reviewed starting **November 16, 2009**, and will be accepted until the position is filled. Please refer to ad #26 on all correspondence. Further information about LID is available at www.niaid.nih.gov/labs/aboutlabs/lid/, information regarding the DIR laboratories is available at www.niaid.nih.gov/about/organization/dir/default.htm, and information about working at NIAID is available at www.niaid.nih.gov/careers/nlc.



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



National Institute of Allergy and Infectious Diseases

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THE NIH IS DEDICATED TO BUILDING A DIVERSE COMMUNITY IN ITS TRAINING AND EMPLOYMENT PROGRAMS



WWW.NIH.GOV

Tenure-Track/Tenured Investigator Laboratory of Immunology

The Laboratory of Immunology (LI), Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) invites applications for a tenure-track/tenured investigator position in immunology. Applicants should have a Ph.D., M.D., or equivalent degree; an outstanding record of postdoctoral accomplishment; and an interest in any area of biomedical research related to immunology.

Specifically, we seek a highly creative individual who will establish an independent, world-class research program that takes full advantage of the special opportunities afforded by the stable, long-term funding of the intramural research program at NIH. She or he should be interested in developing and applying novel approaches to the study of problems of major biological and/or medical importance, which could include a significant clinical or translational effort in addition to bench research. In the former case, the successful candidate would have access to the NIH Clinical Center, a state-of-the-art research hospital on the NIH campus in Bethesda, MD, and ample opportunity to participate in the activities of the Trans-NIH Center for Human Immunology.

Generous ongoing support for salary, technical personnel, postdoctoral fellows, equipment, and research supplies will be provided. Available core or collaborative facilities include flow cytometry, advanced optical imaging, microarray generation and analysis, high throughput sequencing, computational biology, production of transgenic and gene-manipulated mice, biosafety level (BSL)-3 facilities, chemical genomics, and support for projects involving RNAi screening. The successful applicant will also have access to Trans-NIH initiatives involving technology development, translational investigation, and multidisciplinary science. In addition to an outstanding international postdoctoral community, a superior pool of graduate and undergraduate students is available to the successful applicant.

LI has a distinguished history of accomplishment in immunology. We strongly encourage application by outstanding investigators who can continue and enhance this record of achievement. Current LI investigators are Ronald Germain, Michael Lenardo, David Margulies, Stefan Muljo, William Paul, Ethan Shevach, and Tsan Xiao.

To apply, e-mail curriculum vitae, bibliography, and outline of a proposed research program (no more than two pages) to Ms. Yushekia Hill at NIAID.DIR.Search@niaid.nih.gov. In addition, three letters of reference must be sent directly from the referee to Drs. Giorgio Trinchieri and Dan Kastner, Co-Chairs, NIAID Search Committee, c/o Ms. Yushekia Hill, at NIAID.DIR.Search@niaid.nih.gov or 10 Center Drive, MSC 1356, Building 10, Room 4A22, Bethesda, MD 20892-1356. E-mail is preferred. Applications will be reviewed starting **11/16/09** and will be accepted until the position is filled. Please refer to ad #028 on all communications. For further information about this position, contact Dr. William Paul at 301-496-5046 or wpaul@niaid.nih.gov.

A full package of benefits (including retirement and health, life, and long-term care insurance) is available. Women and minorities are especially encouraged to apply. U.S. citizenship is not required.

National Institute of Allergy and Infectious Diseases

To learn more about NIAID and how you can work in this exciting research organization, please visit us on the web at www.niaid.nih.gov/careers/nti.



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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National Institute of Allergy and Infectious Diseases

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Call for Research Scientists, RIKEN, Japan

RIKEN has openings for research scientists at the following laboratories.

1. Research Department: **Accelerator R&D Team, Accelerator Group** (Group Director: Osamu KAMIGAITO)
[Job Description] http://www.riken.jp/engn/r-world/info/recruit/k091124_e_rnc.html
[Area of Research] <http://www.riken.jp/engn/r-world/research/lab/nishina/acceler/index.html>
2. Research Department: **Atomic, Molecular & Optical Physics Laboratory** (Chief Scientist: Toshiyuki AZUMA)
[Job Description] http://www.riken.jp/engn/r-world/info/recruit/k091124_e_as1.html
[Area of Research] <http://www.riken.jp/engn/r-world/research/lab/wako/optical/index.html>
3. Research Department: **Cellular Informatics Laboratory** (Chief Scientist: Yasushi SAKO)
[Job Description] http://www.riken.jp/engn/r-world/info/recruit/k091124_e_as2.html
[Area of Research] <http://www.riken.jp/engn/r-world/research/lab/wako/cell-info/index.html>
4. Research Department: **Biometal Science Laboratory** (Chief Scientist: Yoshitsugu SHIRO)
[Job Description] http://www.riken.jp/engn/r-world/info/recruit/k091124_e_rsc.html
[Area of Research] <http://www.harima.riken.go.jp/eng/lab0/04.html>

[Conditions] A tenured fulltime position until RIKEN's retirement age of 60. However, the applicant may be offered instead a five-year fixed-term employment contract depending on the selection results. In this case, the employee can move to a tenured position after undergoing a successful review to be held at the end of the first 3 years of employment. Annual salary and other conditions of the fixed-term contract position are the same as for the tenured position. Salary shall be determined on an annual basis subject to the applicant's experience and performance. These and other provisions are in accordance with RIKEN regulations.

[Application] The required documents differ according to the laboratory. Refer to the job description URL mentioned above for details.

[Deadline] 5pm on Tuesday, November 24, 2009 (Japan Standard Time)

[Start of Employment] April 1, 2010 or later, but negotiable.

[Contact Information for Submitting Documents and Making Inquiries]

Research Personnel Section, Advanced Research Promotion Division, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198

E-mail: rps-saiyo (please add "@riken.jp" to complete the address) Email attachments and telephone calls cannot be accepted. When you mail your application, please send as certified mail so that there will be a record of delivery. Please write in red on the front of the envelope, the name of the laboratory you are applying for. <http://www.riken.jp/engn/r-world/info/recruit/index.html>

Faculty Position Molecular Biology Sloan-Kettering Institute

The Molecular Biology Program of the Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center (www.ski.edu), has initiated a faculty search at the Assistant Member level (equivalent to Assistant Professor). We are interested in outstanding individuals who have demonstrated records of significant accomplishment and the potential to make substantial contributions to the biological sciences as independent investigators. Successful applicants will have research interests that move the Program into exciting new areas that complement and expand our existing strengths in the areas of maintenance of genomic integrity, regulation of the cell cycle, and regulation of gene expression. Faculty will be eligible to hold appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

Candidates should e-mail their application in PDF format to: molbio@mskcc.org by **November 16, 2009**. The application should include a CV, description of past and proposed research (3-7 pp), and copies of three representative publications. Candidates should arrange to have three signed letters of reference sent in PDF format to: molbio@mskcc.org. The letters should arrive by **November 16, 2009** and should be addressed to Dr. Kenneth Mariani, c/o Julie Kwan, Box 135, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065. Inquiries may be sent to Ms. Kwan at molbio@mskcc.org or to Dr. Kenneth Mariani, Chair, Molecular Biology Program at kmarians@sloankettering.edu. Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer and smoke-free environment.



Memorial Sloan-Kettering
Cancer Center
www.mskcc.org

DUKE UNIVERSITY MEDICAL CENTER DEPARTMENT OF MOLECULAR GENETICS AND MICROBIOLOGY

Tenure-track Faculty Positions (Assistant/Associate Professor/Professor)

Applications are invited for tenure-track positions in the Department of Molecular Genetics and Microbiology, Duke University Medical Center. We are currently seeking individuals addressing questions of biological interest via genetic and/or microbiological approaches. Existing areas of strength in the department include:

- Microbiology (virology, mycology, bacteriology)
- RNA biology and genomic expression analysis
- Yeast genetics and genomics
- Genetics of model systems and humans
- Chromosome structure, function, replication, and repair

The development of interdisciplinary research and graduate programs at Duke University, including the Institute for Genome Science and Policy, provides a robust environment for scientific interactions and training. Applications should include a curriculum vitae, a description of research accomplishment and plans for future research, and reprints of three representative publications. Applicants should also arrange to have three letters of recommendation submitted on their behalf. Application materials should be emailed as PDF files to: MGMSearch2010@notes.duke.edu.

The deadline for receipt of applications is **December 15, 2009**.

Women and minorities are encouraged to apply. Duke University is an Equal Opportunity/Affirmative Action Employer.

Nobel Laureates and World Academicians converge on **City University of Hong Kong** to discuss topical issues that will shape the future course of science and technology

In celebration of the 25th Anniversary, City University of Hong Kong is staging a series of World Academician Conferences addressing key issues in science. Following the hugely successful opening conference on bioscience, three more fascinating events will examine the advancement of science, energy and environment, and engineering science and technology.

Frontiers in Bioscience:
Learning and Memory
16 June 2009

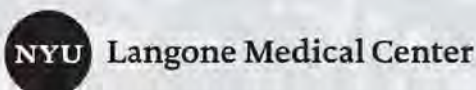
Where is Science Going
in the 21st Century?
22–23 October 2009

Energy and Environment:
Crisis, Opportunities and Challenges
5–6 November 2009

Engineering Science and Technology:
Trends and Frontiers
14–15 December 2009
(in collaboration with the Chinese Academy
of Engineering)



**The Helen L. and Martin S. Kimmel Center
for Biology and Medicine at the Skirball
Institute of Biomolecular Medicine**



Faculty Positions

The Helen L. and Martin S. Kimmel Center for Biology and Medicine at the Skirball Institute of Biomolecular Medicine at New York University Langone Medical Center invites applications for tenure-track positions at the assistant, associate or full professor level. We seek applicants with an exceptional record of achievement who are applying state of the art approaches towards studying complex biological problems.

Successful candidates will join our existing programs in **Developmental Genetics, Molecular Pathogenesis, Structural Biology and Molecular Neurobiology**. These programs are interdisciplinary and reflect strengths at NYU Langone Medical Center and the College of Arts and Sciences. Special priority will be given to applicants who:

- Study mammalian developmental genetics or stem cell biology to understand gene regulation and cellular behavior within an organismal context.
- Study complex physiological circuits, including those that link inflammation to functions of multiple organ systems and that link innate immune responses to host-microbe interactions.
- Study macromolecular structure and mechanism using X-ray crystallography or develop and apply single-molecule techniques.

The NYU Langone Medical Center offers excellent resources to support new faculty, including generous start-up packages and core facilities for cell sorting, imaging, proteomics, mouse molecular genetics, genomics and structural biology.

Successful candidates are expected to initiate and maintain vigorous independent research programs that will enrich and be enriched by the highly collaborative environment at the Skirball Institute and throughout the NYU research community.

This is an electronic application process only. Please create your application packet by formatting it as a single PDF document. Use the following page order: **1) Cover Letter – indicating program preference, 2) Curriculum Vitae, 3) Research Statement 4) One Recent Publication.**

Email the application packet to: skirballsearch@med.nyu.edu by **November 15th, 2009**.

Three letters of reference should be sent independently to: skirballsearch@med.nyu.edu

New York University was founded in 1841 and is an equal opportunity affirmative action employer. Women and minority candidates are encouraged to apply.



<http://skirball.med.nyu.edu/>



**中国科学院上海巴斯德研究所
INSTITUT PASTEUR OF SHANGHAI
CHINESE ACADEMY OF SCIENCES**



(PI Recruitment)

IPS, CAS (<http://www.shanghaipasteur.cas.cn>) is seeking outstanding Principal Investigators (the faculty position) in the fields of **viral immunology and vaccinology**. Candidates working on viral immunology should have strong research backgrounds in **either** human immunology, **or** cellular immunology, **or** viral immunology, **or** mouse model in infectious disease. Candidates working on vaccinology should have proven expertise in at least one of the following areas of vaccine development: DNA or protein or peptide or viral vector or VLP based vaccine platforms, novel adjuvant development, vaccine formulation and delivery, vaccine-related immunology.

Applicants must have a Ph.D. and/or M.D. degree with over four years of postdoctoral training and a track record of publications in high-quality international journals. Successful candidates are expected to develop an independent research program demonstrated by national levels of research funding as well as to teach and to train Ph.D. students. Salary will be highly competitive and commensurate with experiences and qualifications.

IPS, CAS is a newly established institution, co-funded by the Institut Pasteur, the Chinese Academy of Sciences, and the Municipality of Shanghai. IPS offers a large panel of core facilities and excellent working conditions in a highly collaborative environment within the Chinese Academy of Sciences network and the worldwide network of Pasteur Institutes.

To apply, applicants should e-mail a cover letter, curriculum vitae and a brief statement of current and future research goals and the names and addresses of three references to Ms. Caroline Wu at nwu@sibs.ac.cn before **October 31, 2009**



**CENTER FOR CRANIOFACIAL
MOLECULAR BIOLOGY**

The Center for Craniofacial Molecular Biology at the University of Southern California School of Dentistry seeks applicants for two tenure-track appointments at the Assistant Professor level in Craniofacial Developmental Biology and Tissue Regeneration. We invite candidates whose research interests are complementary to our goal of enhancing our understanding of the multidisciplinary events shaping craniofacial morphogenesis, their malformations and the use of stem cell biology for tissue regeneration. For more information visit the CCMB Web site at: <http://www.usc.edu/hsc/dental/ccmb/>. This will be a joint appointment with the USC School of Dentistry and the Keck School of Medicine, permitting access to university wide infrastructural research resources, such as core laboratories and full access to PhD students and postdoctoral fellows. Applicants should have a PhD, DDS/PhD, or MD/PhD degree and vigorous post-doctoral training with high impact publications. The successful candidates will be expected to develop an independent research program and successfully compete for NIH funding.

Interested applicants should send a cover letter, complete curriculum vitae, statement of current and future research plans and arrange to have at least three letters of recommendation sent to:

Dr. Yang Chai, Search Committee Chair
c/o Ms. Patricia Thompson
Center for Craniofacial Molecular Biology
USC School of Dentistry
2250 Alcazar Street, CSA 103
Los Angeles, CA 90033

Email: pathomps@usc.edu; Fax: (323)442-2981

*The University of Southern California values diversity
and is committed to equal opportunity in employment.*

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Join the Network.

Year-long fellowships are available in the U.S. Congress and federal agencies. Applicants must hold a PhD or equivalent doctoral-level degree in any behavioral/ social, biological, computational/ mathematical, earth, medical/health, or physical science, or any engineering discipline. Individuals with a master's degree in engineering and three years of post-degree professional experience also may apply. Federal employees are not eligible and U.S. citizenship is required.

Apply.

The application deadline for the 2010-2011 AAAS Fellowships is 15 December 2009. Fellowships are awarded in the spring and begin in September. Stipends range from \$73,000 to \$95,000.

Note: Additional fellowships are available through approximately 30 scientific society partners. Individuals are encouraged to apply with AAAS as well as with any scientific societies for which they qualify.

Full details at: **fellowships.aaas.org**



*Enhancing Public Policy,
Advancing Science Careers*

Krista Donaldson, PhD

Mechanical Engineering,
Stanford University

2004-05 AAAS Fellow at the
U.S. Department of State,
Bureau of Near Eastern
Affairs, Iraq Desk, Economic
Section

Now a researcher in
engineering design at
Stanford University's Center
for Design Research



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SCHOOL OF MINES
& TECHNOLOGY

Provost/Vice President for Academic Affairs

The South Dakota School of Mines and Technology invites applications for the position of Provost/Vice President for Academic Affairs. The successful candidate will provide leadership for all areas of Academic Affairs, including academic programs, academic budget development and resource allocation, faculty development, enrollment management, institutional and program assessment, the library, and information technology services. The Provost/Vice President for Academic Affairs reports directly to the School's President and assists the President in developing the School's four strategic foci: optimizing enrollment; growing graduate programs and the research enterprise; securing resources; and, continuous quality improvement. He/she serves on the President's Executive Council and Institutional Cabinet, co-chairs the Institutional Academic Advisory Board, and serves as the interim president during presidential absences. Additionally, the Provost/Vice President for Academic Affairs is the institutional representative to the state-wide Academic Affairs Council.

The successful applicant will possess an earned doctorate (with a preference given to Engineering or Science) from an accredited university with a record of teaching and scholarship sufficient to warrant a tenured appointment at the rank of full professor. In addition, he/she should have at least five years of related administrative experience with demonstrated senior administrative capability; the ability to effectively represent the university locally and internationally; strong interpersonal and communication skills; a demonstrated commitment to fostering excellence in research and teaching; leadership skills in academic program development, assessment, accreditation, strategic planning, technology implementation, and faculty development; strong financial management experience as well as an ability to make data-based decisions within resource limitations; a demonstrated commitment to diversity in hiring, including affirmative action and equal opportunity, and the fostering of an ethnically and culturally diverse learning community; knowledge of key and emerging higher education issues; an ability to work collaboratively with diverse constituencies and an understanding and respect for traditions of shared governance.

The School of Mines is a public state university offering baccalaureate, masters, and doctoral degrees in science and engineering with a student population of approximately 2,100 traditional and non-traditional learners representing 40 states and 29 countries. The university is located at the foot of the beautiful Black Hills in Rapid City, South Dakota's second largest city. Twenty-five miles from Mount Rushmore, Rapid City has a relatively mild climate and the Black Hills offer numerous opportunities for summer and winter outdoor experiences. For more information regarding Rapid City and the university, visit: <http://visitrapidity.com/> and www.sdsmt.edu.

The School of Mines is committed to recruiting and retaining a diverse workforce. To apply for this position, applicants must apply on-line at <http://sdmines.sdsmt.edu/sdsmt/employment>. If you need an accommodation to the on-line application process, please contact Human Resources (605) 394-1203. Review of applications will begin **October 26, 2009**, and will continue until the position is filled.

SDSMT is an EEO/AA/ADA Employer and Provider.



Center for stem cell biology

The University of Michigan invites applications for tenure track **ASSISTANT PROFESSOR** positions. We are seeking outstanding scholars, with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in any aspect of stem cell biology. Applicants who have already established successful independent research programs will be considered for tenured **ASSOCIATE PROFESSOR** or **PROFESSOR** positions.

Applicants should send a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly by **October 31, 2009** to: **Stem Cell Search Committee, c/o Rebecca Fritts, Life Sciences Institute, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan, 48109-2216.**

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.



"The Future Grows Here"

SUPERVISORY RESEARCH ENTOMOLOGIST/CHEMIST/ OR PLANT PATHOLOGIST

**Commodity Protection and Quality
Research Unit, Parlier, CA
GS14/15; Salary Range of
\$95,010.00 to \$145,290.00**

The USDA, Agricultural Research Service (ARS) is seeking an outstanding research scientist for a permanent full-time Research Leader position. The incumbent will lead a multi-disciplinary team of scientists to develop effective postharvest commodity protection strategies to mitigate the effects of insect pests, including production pests when these subsequently become postharvest pests, on horticultural crops including fresh or dried fruit/vegetables and nuts. The incumbent will develop an individual research program in postharvest entomology, microbiology, plant physiology, chemistry or biochemistry that contributes to the research objectives of the Unit to maintain/enhance postharvest commodity quality, and developing new and improved postharvest pest control technology or methodology to meet domestic and foreign export market requirements. U.S. citizenship is required. A PhD is highly desirable. To apply, print a copy of vacancy announcement **ARS-X9W-0256** from the ARS Careers Website at <http://www.afm.ars.usda.gov/divisions/hrd/index.html> and follow the application directions provided. For questions about this position, call **Dr. Edwin Civerolo**, at 559-596-2702 or E-Mail: Edwin.civerolo@ars.usda.gov Applications must be received by **October 16, 2009**. *USDA/ARS is an Equal Opportunity Employer and Provider.*



The Argonne Named Postdoctoral Fellowship Program

The Director's Office initiated these special postdoctoral fellowships at Argonne, to be awarded internationally on an annual basis to outstanding doctoral scientists and engineers who are at early points in promising careers. The fellowships are named after scientific and technical luminaries who have been associated with Argonne and its predecessors, and the University of Chicago, since the 1940s.

Candidates for these fellowships must display superb ability in scientific or engineering research, and must show definite promise of becoming outstanding leaders in the research they pursue. Fellowships are awarded for a two-year term, with a possible renewal for a third year, and carry a stipend of \$78,000 per annum with an additional allocation of up to \$20,000 per annum for research support and travel.

Requirements for applying for an Argonne Named Postdoctoral Fellowship:

The following documents must be sent via e-mail to Named-Postdoc@anl.gov by November 2, 2009. In the subject line please include the name of the candidate.

- Nomination memo (≤ 2 pages) from ANL sponsor
- Research proposal (≤ 2 pages)
- Three letters of recommendation from other than Argonne staff
- CV
- List of publications, abstracts and significant presentations
- Graduate school transcripts

The sponsor could be someone who is already familiar with your research work and accomplishments through previous collaborations of professional societies. If you have not yet identified an ANL sponsor, visit the detailed websites of the various Research Programs and Research Divisions at www.anl.gov.

All correspondence should be addressed to Argonne Named Postdoctoral Fellowship Program. One application is sufficient to be considered for all named fellowships. For additional details, visit the Argonne website at <http://www.dep.anl.gov/postdocs/>. Argonne is an equal opportunity employer and we value diversity in our workforce.

Argonne is a U.S. Department of Energy laboratory managed by UChicago Argonne, LLC

J. Craig Venter Institute Faculty Positions

For nearly two decades our scientists have been at the forefront of the genomic revolution. Now, we want you to join us in our quest.

J. Craig Venter Institute scientists have been unraveling and understanding the complexities of life as contained in the genomes of thousands of microbes, plants, and mammals, including humans. Our scientific success is built on the philosophy of conducting science boldly in new interdisciplinary ways, using new tools and with the best scientists. The ever increasing amounts of genomic data and new avenues of research to explore, mean we need additional scientists with unique skills and ideas that will help us better understand the world around us.

JCVI is seeking qualified applicants for positions at all levels in both our Rockville, Maryland headquarters and our San Diego, California facility. We're looking for interested candidates in the following research areas:

- Human genomics
- Environmental genomics, including human microbiome research
- Synthetic genomics
- Infectious Disease
- Bioenergy

Successful candidates will conduct innovative, independent research, obtain extramural funding, take advantage of interactions with our interdisciplinary, highly collegial group of scientists within JCVI, and complement existing strengths within the organization. Candidates must have a Ph.D. or M.D. and a record of accomplishment in one or more of the targeted areas. The level of appointment will be commensurate with experience. Candidates will be provided with a start-up package.

JCVI offers an excellent working environment and a competitive benefits package. Interested applicants should apply directly in our career center by submitting their CV and a cover letter which includes a description of research interests and contact information for three references. JCVI's Career Center is located on our web site at www.jcvi.org

Equal Opportunity Employer M/F/D/V





Tenure Track Faculty Position in Biochemistry

The Division of Molecular Biology and Biochemistry, School of Biological Sciences, University of Missouri-Kansas City invites applications for a full-time tenure-track faculty position at a rank commensurate with prior experience and accomplishments. Candidates for a mid-level or senior appointment should have an established record of research productivity and extramural funding. Outstanding scientists in contemporary or emerging areas of biochemical research are encouraged to apply. We seek outstanding scholars with demonstrable abilities in research and teaching, as well as exemplary communication skills. Faculty appointments in the School of Biological Sciences offer competitive salaries, laboratory space, and start-up funds. Core instrumentation facilities support research in macromolecular crystallography, biomolecular NMR, proteomics, and genomics.

Applicants should forward a *curriculum vitae*, reprints of 2-3 recent publications, and a summary of current and future research plans to the address listed below. Alternatively, electronic copy of application materials (MS Word or Adobe pdf) may be submitted to: mbbsearch@umkc.edu. Subject line should indicate: MBB faculty search. Three letters of recommendation should be directly transmitted to the search committee by the candidate's referees. Application review will begin immediately and will continue until the position is filled. **MBB Search Committee, Division of Molecular Biology and Biochemistry – BSB503, University of Missouri-Kansas City, 5007 Rockhill Road, Kansas City, MO 64110-2499.**

The University of Missouri-Kansas City is an EO/AA Employer.



Professor and Head Division of Cell Biology and Biophysics

Applications are invited for Professor and Head of the Division of Cell Biology and Biophysics at the School of Biological Sciences, University of Missouri-Kansas City. The successful candidate should have a record of excellence in research with sustained extramural funding. The candidate will be expected to play a leadership role in graduate and undergraduate education, faculty mentorship, determining future research directions, and in the overall development and growth of the School. The School of Biological Sciences is positioning itself to become a regional leader in the areas of structural, molecular, and cellular biology, and microbiology, and welcomes applications from qualified candidates in those areas. However, outstanding scientists from all areas of basic life sciences are encouraged to apply. The successful candidate will receive a competitive 12-month salary, renovated research space, a start-up package commensurate with rank, and the availability of excellent research support facilities within the School of Biological Sciences. Candidates should have a Ph.D. and currently hold a tenured academic position at the rank of Professor.

To apply, please submit electronically (MS Word or pdf) a CV, a statement of present and future research interests, and the names and addresses of 3 references to: **Ms. Micaela Escareno** (escarenom@umkc.edu). All materials will be handled with strict confidentiality. The position will remain open until filled.

UMKC is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.



Faculty Position in Immunology

The Department of Molecular Genetics and Microbiology at the University of New Mexico School of Medicine (<http://hsc.unm.edu/som/micro/>) is seeking an Assistant Professor (exceptional cases at Full Professor will be considered) to join a new program in T cell biology. The successful applicant will be an active participant in departmental activities including medical school teaching. Salary and rank commensurate with qualifications and experience.

Minimum Requirements: • Ph.D., M.D. or equivalent • 2 years of post-graduate research experience in immunology • eligible to work in the United States

Desirable Qualifications:

- strong record of scientific accomplishments
- high probability of receiving external funding
- potential for research and educational interactions with members of the Department of Molecular Genetics and Microbiology
- potential synergy with UNM Health Sciences Center signature programs (hsc.unm.edu/som/bmb/Signature%20Research%20Prgrms/infectious_diseases_and_immunity.shtml)

UNM places a high priority on the success of its junior faculty. The successful applicant will be given protected time and mentoring by senior faculty to ensure success in extramural funding.

Applicants must submit a CV, a letter addressing career goals and qualifications, a brief research plan including a clearly stated significance section and the names of 3 references to: **Dolores Tarín, Department Administrator, MSC08 4660, 1 University of New Mexico, Albuquerque, NM, 87131.** Reference job posting **PRC 677**. For best consideration apply by **December 1, 2009**. The position will remain open until filled.

UNM is an Equal Opportunity/Affirmative Action Employer and Educator.

Evolutionary Developmental Biology Assistant/Associate/Professor School of Biological Sciences, College of Sciences Washington State University Search #5231

The School of Biological Sciences at Washington State University, Pullman, Washington, invites applications for a full-time, permanent, tenure-track faculty position in Animal Evolutionary Developmental Biology to begin August of 2010. Rank for this position is open at Assistant or Associate Professor or Professor. Candidates should have a record that demonstrates relevant ability in animal organismal and evolutionary biology, collaborative research and training, and that complements our faculty's strengths in organismal and evolutionary biology, molecular evolution, population and ecological genetics, systematics, ecology, and physiology. Applicants must show evidence, commensurate with rank, of outstanding teaching and the development and maintenance of an internationally recognized, extramurally funded empirical research program in animal evolutionary developmental biology. Candidates who are pursuing rigorous, theory-driven empirical research using sophisticated analytical tools are encouraged to apply.

Required qualifications include an earned doctorate at time of application, a record of research accomplishment commensurate with rank in evolutionary developmental biology of animals, evidence of a commitment to teaching excellence in undergraduate and graduate courses and effective communication skills. Successful candidates will be expected to develop and maintain a vigorous, independent research program supported by extramural funding, train graduate and undergraduate students, participate in graduate and undergraduate teaching, and advance the college's commitment to diversity and multiculturalism.

To apply, send a letter of application addressing qualifications, a curriculum vitae, and teaching and research statements. In addition, please provide the names, addresses, and contact information of at least three references that can address research history and teaching and communication skills. Review of applications begins **October 25, 2009**. Send all materials electronically (PDF) to: **Evolutionary Developmental Biology Search Committee, c/o Linda Larrabee; larrabee@wsu.edu; Phone: (509) 335-5768**. Full notice of vacancy can be viewed at <http://www.hrs.wsu.edu/employment/fapvacancies.aspx>. For information on the status of your application, please contact **Linda Larrabee** at (509) 335-5768 or larrabee@wsu.edu.

EEO/AA/ADA



UNIVERSITY OF MICHIGAN

SCHOLARS PROGRAMS

BIOLOGICAL SCIENCES SCHOLARS PROGRAM For Junior, Tenure-Track Faculty

The University of Michigan announces recruitment for the Biological Sciences Scholars Program (BSSP) to continue to enhance its investigational strengths in the life sciences research programs.

Now entering its 13th year, this Program has led to the recruitment of outstanding young scientists in the areas of genetics, microbiology, immunology, virology, structural biology, pharmacology, biochemistry, molecular pharmacology, stem cell biology, cancer biology, physiology, cell and developmental biology, and the neurosciences. The Program seeks individuals with PhD, MD, or MD/PhD degrees, at least two years of postdoctoral research experience, and evidence of superlative scientific accomplishment and scholarly promise. Successful candidates will be expected to establish a vigorous, externally-funded research program, and to become leaders in departmental and program activities, including teaching at the medical, graduate, and/or undergraduate levels. Primary college and department affiliation will be determined by the applicant's qualifications and by relevance of the applicant's research program to departmental initiatives and focus. All faculty recruited via the BSSP will be appointed at the Assistant Professor level.

APPLICATION INSTRUCTIONS: Please apply to the Scholars Program through the BSSP website at: (<http://www.med.umich.edu/medschool/research/bssp/>). A curriculum vitae (including bibliography), a three-page research plan, an NIH biosketch, and three original letters of support should all be submitted through the BSSP website. More information about the Scholars Program, instructions for applicants and those submitting letters of recommendation, and how to contact us is located on the BSSP web site: (<http://www.med.umich.edu/medschool/research/bssp/>). The deadline for applications is Friday, October 30, 2009.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.



ASSISTANT PROFESSOR Cardiovascular Division

The Department of Medicine, Cardiovascular Division is seeking applications for a tenure-track faculty position at the Assistant Professor level. Qualified candidates must have a M.D., M.D./Ph.D. or Ph.D. degree(s) and productive lab research experience. Areas of research considered to be a priority are: cardiac excitation-contraction coupling, cardiac calcium channel physiology, and cardiovascular nitric oxide signaling. The successful candidate will be expected to build and maintain an active, externally financed research program that complements the current research standards set by the Department/Division. A competitive salary and startup package will be provided.

Individuals interested in applying for this position are encouraged to submit their curriculum vitae with a cover letter describing teaching philosophies and goals, along with three letters of reference to: **Anthony J. Muslin, M.D., Chair of the Search Committee, Cardiovascular Division, Washington University, School of Medicine, 660 S. Euclid Ave., Campus Box 8086, St. Louis, Missouri 63110.** The application review process will begin **October 1, 2009**, and will continue until the position is filled.

Washington University is an Equal Opportunity and Affirmative Action Employer. Women and minorities are encouraged to apply.



Department of Health and Human Services
National Institutes of Health
National Institute of Dental and Craniofacial Research



CLINICAL DIRECTOR

The National Institute of Dental and Craniofacial Research (NIDCR) invites applications for the position of Clinical Director in the Division of Intramural Research. The incumbent is responsible for all patient-related activities in the NIDCR intramural program at the Bethesda campus, serves as a representative for NIDCR with the National Institutes of Health (NIH) Clinical Center, advises the Scientific Director and the Institute Director in the planning and development of a clinical research portfolio, and provides direction to all clinical intramural programs and activities (training and research). The Clinical Director provides leadership to the development and administration of NIDCR clinical training programs, oversees the Clinical Research Core Facility, and administers quality assurance programs for all clinical and translational research and patient-related activities. In addition, he/she acts as liaison to senior and junior clinical staff and the public.

Qualifications for this position include a DDS/DMD degree. The successful candidate must have a national/international reputation as an exceptional medical scientist and be prepared to establish an independent clinical and/or translational research program within NIDCR. In addition, the candidate must have demonstrated administrative, management, leadership and mentoring skills. Women and minorities are encouraged to apply.

The NIDCR is a major research component of the NIH and the Department of Health and Human Services (DHHS). Current research programs at NIDCR include: basic and translational biology of bone and teeth; physiology and developmental biology of salivary glands and novel approaches to treatment of salivary hypofunction; etiology and treatment of oral and pharyngeal cancer; inflammation, oral biofilms and infectious diseases; craniofacial genetics; and the neurobiology of taste, pain and touch. With nation-wide responsibility for improving the health and well being of all Americans, the DHHS oversees the biomedical research programs of the NIH and those of NIH's research Institutes.

Interested candidates should send a cover letter, curriculum vitae, bibliography, and names and complete contact information for three references to: Ms. Carol Beasley, National Institute of Dental and Craniofacial Research, 31 Center Drive, Building 31, Room 2C39, MSC-2290, Bethesda, MD 20892-2290 or via email to carol.beasley@nih.gov. Applications will be considered until the position is filled.

DHHS and NIH are Equal Opportunity Employers



Lennox K. Black International Prize For Excellence In Biomedical Research

Thomas Jefferson University, an academic health center and premier research institution in Philadelphia, Pennsylvania, solicits nominations for the 2010 Recipient of the Lennox K. Black Prize. The Prize is awarded biennially and recognizes the impact, accomplished or potential, of pioneering biomedical research on the alleviation of human disease and suffering.

The 2010 Prize will recognize major contributions toward a mechanistic understanding, control, therapy or prevention of Infectious Diseases.

The Black Prize awardee will be keynote speaker at a symposium at Thomas Jefferson University in November, 2010, and will receive the Black Prize Medal and cash award of US\$15,000. We invite nominations of internationally

recognized biomedical scientists residing outside the United States. Nominations, which should include a full curriculum vitae and brief statement of research accomplishments and contributions, should be received by 29 October 2009.

Please direct nominations or inquiries to:

Laurence Eisenlohr, VMD, PhD or James H. Keen, PhD
Co-Chairs, Selection Committee
c/o Jefferson College of Graduate Studies
1020 Locust Street, M-63
Philadelphia, PA 19107
USA

Telephone: 215-503-8982

Email: Laurence.Eisenlohr@jefferson.edu

THOMAS JEFFERSON UNIVERSITY



The University of Texas at Austin

Endowed Chair Position

The Institute for Cellular and Molecular Biology

The Institute for Cellular and Molecular Biology invites applications for an Endowed Chair Position. An academic appointment at the level of tenured Professor will be held in an appropriate academic unit in the College of Natural Sciences. Candidates should have an outstanding research program that applies molecular biological and/or biochemical approaches to important biological problems. Areas of interest include, but are not limited to, Biochemistry, Cancer Biology, and Human Genetics. The position carries an exceptional salary and start-up package.

Building on a strong existing faculty, the Institute has recruited more than 60 new faculty members in the past ten years. Faculty roster can be reviewed at <http://www.icmb.utexas.edu>. In addition to its highly interactive and interdisciplinary research environment, The Institute is the home base for the University-wide Graduate Program in Cell and Molecular Biology and supports the state-of-the-art core facilities for DNA and protein analysis, mass spectrometry, electron and confocal microscopy, DNA microarrays, robotics, X-ray crystallography, mouse genetic engineering, and NexGen genomic sequencing. An MD-PhD program with the UT Medical Branch and the new Dell Pediatrics Research Institute in Austin further enhance the environment for Biomedical Research.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and livable cities.

Please send curriculum vitae, summary of research interests, and names of five references to:

Dr. Alan M. Lambowitz, Director
The Institute for Cellular and Molecular Biology
The University of Texas at Austin
1 University Station A4800
Austin TX 78712-0159

The University of Texas at Austin is an Equal Opportunity Employer. Qualified women and minorities are encouraged to apply; a background check will be conducted on applicant selected.



Why not change the world?

Assistant Professor - Biology

The Department of Biology at Rensselaer Polytechnic Institute in Troy, NY is in a period of rapid expansion with many new faculty appointments in a wide spectrum of areas in the biological sciences anticipated in the next five years. Currently, the Department is actively seeking an exceptionally qualified scientist to work in an exciting, interdisciplinary environment as a full-time tenure-track assistant professor.

Qualifications: The successful candidate will have

- A Ph.D. or equivalent degree in the biological sciences (degree must be conferred by the commencement of the appointment)
- Related postdoctoral experience
- Demonstrated, through accomplishments, promise of future distinction in scholarship and education

Expectations: As a member of Rensselaer's tenure track faculty, the incumbent will be expected to establish an extramurally funded research program, to train graduate students, and to participate in undergraduate education.

Application Instructions: To apply, applicants should email a single PDF document containing curriculum vitae, a three-page statement of research accomplishments and goals, and a brief description of teaching interests to biology-chair@rpi.edu. In addition, applicants should arrange to have at least three letters of recommendation forwarded by email. Consideration of candidates will begin upon receipt of applications and will continue until the position is filled.



Rensselaer

We welcome candidates who will bring diverse intellectual, geographical, gender and ethnic perspectives to Rensselaer's work and campus communities. Rensselaer Polytechnic Institute is an Affirmative Action/Equal Opportunity Employer.

**2009 MRS**

fall meeting

Boston, MA November 30-December 4

SYMPOSIA

INFORMATION PROCESSING AND SENSING

- A: High-k Dielectrics on Semiconductors with High Carrier Mobility
- B: Reliability and Materials Issues of Semiconductor Optical and Electrical Devices
- C: Large-Area Processing and Patterning for Optical, Photovoltaic, and Electronic Devices II
- D: Organic Materials for Printable Thin-Film Electronic Devices
- E: Advanced Materials for Half-Metallic and Organic Spintronics
- F: Multiferroic and Ferroelectric Materials
- G: Magnetic Shape Memory Alloys
- H: ZnO and Related Materials
- I: III-Nitride Materials for Sensing, Energy Conversion, and Controlled Light-Matter Interactions
- J: Diamond Electronics and Bioelectronics—Fundamentals to Applications III

NANOSCIENCE AND TECHNOLOGY

- K: Nanotubes and Related Nanostructures
- L: Large-Area Electronics from Carbon Nanotubes, Graphene, and Related Noncarbon Nanostructures
- M: Multifunction at the Nanoscale through Nanowires
- N: Colloidal Nanoparticles for Electronic Applications—Light Emission, Detection, Photovoltaics, and Transport
- O: Excitons and Plasmon Resonances in Nanostructures II
- P: The Business of Nanotechnology II

ENERGY AND THE ENVIRONMENT

- Q: Photovoltaic Materials and Manufacturing Issues II
- R: Advanced Nanostructured Solar Cells
- S: Organic Materials and Devices for Sustainable Energy Systems
- T: Nanomaterials for Polymer Electrolyte Membrane Fuel Cells
- U: Materials Challenges Facing Electrical Energy Storage
- V: Materials Research Needs to Advance Nuclear Energy
- W: Hydrogen Storage Materials
- Y: Catalytic Materials for Energy, Green Processes, and Nanotechnology
- Z: Energy Harvesting—From Fundamentals to Devices

- AA: Renewable Biomaterials and Bioenergy—Current Developments and Challenges
- BB: Green Chemistry in Research and Development of Advanced Materials

MATERIALS ACROSS THE SCALES

- CC: Phonon Engineering for Enhanced Materials Solutions—Theory and Applications
- DD: Microelectromechanical Systems—Materials and Devices III
- EE: Metamaterials—From Modeling and Fabrication to Application
- FF: Mechanical Behavior of Nanomaterials—Experiments and Modeling
- GG: Plasticity in Confined Volumes—Modeling and Experiments
- HH: Multiscale Polycrystal Mechanics of Complex Microstructures
- II: Mechanochemistry in Materials Science
- JJ: Multiscale Dynamics in Confining Systems
- KK: Nanoscale Pattern Formation
- LL: Multiphysics Modeling in Materials Design
- MM: Ultrafast Processes in Materials Science
- NN: Advanced Microscopy and Spectroscopy Techniques for Imaging Materials with High Spatial Resolution
- OO: Dynamic Scanning Probes—Imaging, Characterization, and Manipulation
- PP: Materials Education

HEALTH AND BIOLOGICAL MATERIALS

- QQ: Responsive Gels and Biopolymer Assemblies
- RR: Engineering Biomaterials for Regenerative Medicine
- SS: Biosurfaces and Biointerfaces
- TT: Nanobiotechnology and Nanobiophotonics—Opportunities and Challenges
- UU: Molecular Biomimetics and Materials Design
- VV: Micro- and Nanoscale Processing of Biomaterials
- WW: Polymer Nanofibers—Fundamental Studies and Emerging Applications
- XX: Biological Imaging and Sensing Using Nanoparticle Assemblies
- YY: Compatibility of Nanomaterials

GENERAL INTEREST

- X: Frontiers of Materials Research

2009 MRS Fall Meeting Chairs

Kristi Anselth

University of Colorado
Tel 303-735-5336
kristi.anselth@colorado.edu

Li-Chyong Chen

National Taiwan University
Tel 886-2-33665249
chenlc@ntu.edu.tw

Peter Gumbsch

University of Karlsruhe (TH)
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—and—
Fraunhofer-Institut fuer
Werkstoffmechanik IWM
Tel 49-761-5142-100
peter.gumbsch@iwf.fraunhofer.de

Ji-Cheng Zhao

The Ohio State University
Tel 614-292-9462
zhao.199@osu.edu



Member Services
Materials Research Society
506 Keystone Drive
Warrendale, PA 15086-7573

Tel 724-779-3003
Fax 724-779-8313
info@mrs.org

For additional meeting information, visit www.mrs.org/fall2009

POSITIONS OPEN



FACULTY POSITIONS at The Lilliehei Heart Institute, University of Minnesota

The Lilliehei Heart Institute at the University of Minnesota–Minneapolis seeks exceptional, interactive and creative physician-scientists and scientists to join our faculty. We invite applications from outstanding candidates for tenure-track positions (**ASSISTANT** and **ASSOCIATE PROFESSOR**) as well as tenured faculty. The positions offer outstanding startup funds, highly competitive salaries, new laboratory space, and access to outstanding state-of-the-art core facilities in an interactive and collaborative environment. Of particular interest are candidates having a research focus in cardiac morphogenesis, stem cell and iPSC biology, signaling pathways in hypertrophy and heart failure, cardiovascular genomics, microRNAs and molecular physiology. Interested applicants should provide curriculum vitae and a two- to five-page statement of current research interests and future plans and should have three letters of recommendation sent directly to the following address:

Daniel J. Garry, M.D., Ph.D.
Chief, Cardiovascular Division
Director, Lilliehei Heart Institute
312 Church Street S.E., Room 4-112 NHH
University of Minnesota
Minneapolis, MN 55455
E-mail: garry@umn.edu

*The University of Minnesota is an Affirmative Action/
Equal Opportunity Employer.*

The Department of Biological Sciences ([website: http://www.biology.buffalo.edu](http://www.biology.buffalo.edu)) at the State University of New York at Buffalo (UB) is seeking outstanding applicants for a tenure-track **ASSISTANT PROFESSOR** position in the field of developmental genomics. Candidates with interests in using whole-genome approaches in animals and/or plants to study fundamental biological processes including embryonic development, nervous system development, and creation/maintenance of specific organs and tissues are encouraged to apply. This position is offered as part of a strategic initiative in the area of molecular recognition in biological systems and bioinformatics.

UB is the largest and most comprehensive campus in the SUNY system. We offer outstanding research facilities with opportunities for interdisciplinary interactions within UB, Roswell Park Cancer Institute, and the New York State Center of Excellence in Bioinformatics and Life Sciences. A generous startup package will be provided. The successful candidate will be expected to maintain an externally funded research program and to participate in graduate and undergraduate teaching. Applicants should have a Ph.D. (or other Doctorate degree), at least three years of postdoctoral experience, a scholarly publication record, and fluency in both spoken and written English.

To apply, curriculum vitae, description of current and future research interests, and reprints of at least three recent or in-press publications must be electronically submitted to [website: http://www.ubjobs.buffalo.edu/applicants/Central/quickFind=52921](http://www.ubjobs.buffalo.edu/applicants/Central/quickFind=52921). In addition, three reference letters should be sent under separate cover, either electronically to e-mail: devgenomics-search@buffalo.edu, or by mail to: Developmental Genomics Search Committee, Department of Biological Sciences, 109 Cooke Hall, University at Buffalo, Amherst, NY 14260. Applications should be received by November 1, 2009. Review of applications will continue until the position is filled. Please consult our website for information about UB, our Department, and our community.

The University at Buffalo is an Equal Opportunity Employer/Recruiter.

POSITIONS OPEN

The University of Nebraska–Lincoln, Institute of Agriculture and Natural Resources, invites applications for a 12-month, tenure-track position at the **ASSISTANT PROFESSOR** level in horticulture. The position is in the Department of Agronomy and Horticulture, located at the West Central Research and Extension Center, North Platte, Nebraska, with 50 percent research and 50 percent extension responsibilities. Applicants must have a Ph.D. in place by date of hire in horticulture, botany, or breeding as well as demonstrated competency in leading a successful research program including obtaining grants and publishing research results and in extension programming through leading workshops and outreach publications. Successful candidate will develop a competitive grant-funded research program in sustainable horticultural practices focusing on irrigation/drought stress/water conservation through cultural practices, selection and/or breeding of native ornamental plants/specialty horticultural crops using modern genetic modifications. Successful candidate will work on extension teams to serve a diverse clientele including home owners, public institutions, commercial firms, growers of specialty crops, policy makers, grower cooperatives, and University of Nebraska extension educators, and to provide leadership in developing and updating recommendations for sustainable practices in landscapes and plant selections ideally suited for the northern Great Plains.

To apply, go to [website: http://www.unl.edu/employment](http://www.unl.edu/employment). Search for requisition #090541 and complete the Faculty Academic Administrative Information Form. Attach a letter of application and curriculum vitae, and arrange for three letters of reference to be sent electronically to e-mail: cwendt1@unl.edu by October 23, 2009. Review of applications will begin on October 23, 2009, and continues until the position is filled or the search is closed. *The University of Nebraska has an active National Science Foundation ADVANCE gender equity program, and is committed to a pluralistic campus community through affirmative action, equal opportunity, work-life balance, and dual careers.*

ASSISTANT PROFESSOR in Quantitative Biology

Oakland University is seeking an outstanding researcher in quantitative biology, starting January 1, 2010. Applicants from a wide variety of disciplines are welcome, including bioinformatics, mathematical modeling, biostatistics, and bioengineering. Applicants should possess a Ph.D. in mathematics, biology, engineering, or a closely related field to the area of quantitative biology, and preferably additional postdoctoral experience. Teaching experience at the college level, or the potential to be an outstanding teacher, and extensive research experience in the area of quantitative biology are required. The faculty member will be hired into a department that best fits the background of the applicant, such as mathematics and statistics, biological sciences, or electrical and computer engineering. Candidates for this position must engage in interdisciplinary research that crosses department boundaries, and must use mathematical or numerical methods to solve important biomedical problems. The applicant will initially focus on developing a world-class, externally funded research program. In the long term, the applicant should have the potential to become a researcher/educator who can help establish and lead a planned quantitative biology Ph.D. program. The ideal candidate should fit well with several of the established strengths at Oakland University, and should be able to contribute to biomedical research at the new Oakland University William Beaumont School of Medicine. Applicants should submit curriculum vitae along with a description of research interests, and should arrange for three letters of reference to be sent to: Dr. Brad Roth, Quantitative Biology Search Committee, Department Physics, Oakland University, Rochester, MI 48309. Or submit electronically to e-mail: roth@oakland.edu. To receive full consideration, applications should be received by October 15, 2009. *Oakland University is an Equal Opportunity Employer. Women and minorities are encouraged to apply.*

POSITIONS OPEN



FACULTY POSITIONS Organismal Physiology Cell and Developmental Biology University of Washington

As part of a long-term hiring plan, the Department of Biology ([website: http://www.biology.washington.edu](http://www.biology.washington.edu)) is conducting a search for outstanding scientists in all areas of biology. To enhance a forward-looking faculty while maintaining traditional excellence, we encourage applications this year from candidates working in organismal physiology, cell and developmental biology, or novel syntheses of these areas. A record of outstanding achievement, a promising research program, and a commitment to teaching are more important than the specific research topic or study organism. Tenure-track appointments at the **ASSISTANT** or **ASSOCIATE PROFESSOR** rank are anticipated. Priority will be given to applications received by 15 October 2009 at [website: http://www.biology.washington.edu/fachires/](http://www.biology.washington.edu/fachires/). Applicants must have earned a doctorate by the date of appointment. All University of Washington faculty engage in teaching, research, and service. *UW is an Affirmative Action, Equal Opportunity Employer. We have a culturally diverse faculty and staff and strongly encourage applications from women, minorities, individuals with disabilities, and covered veterans.*

The Instituto de Neurobiología-Universidad Nacional Autónoma de México in Querétaro, Mexico ([website: http://www.inb.unam.mx](http://www.inb.unam.mx)), invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level in the Department of Developmental Neurobiology and Neurophysiology. We seek scientists whose research focuses on one or more of the following themes using modern and novel experimental approaches: development of the nervous system; structure, connectivity, and plasticity of the nervous system; sensory systems; chronobiology; aging; neurodegeneration; and stem cells. The successful applicant will be expected to establish a strong, externally funded research program, to engage in intramural collaborative projects, to supervise graduate students, and to teach basic and advanced courses in the area of neurobiology. Applicants should send their curriculum vitae, three letters of recommendation, vision statements on research and teaching, and selected publications to: Magda Giordano, e-mail: giordano@servidor.unam.mx by October 31, 2009.

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October 14, 2009

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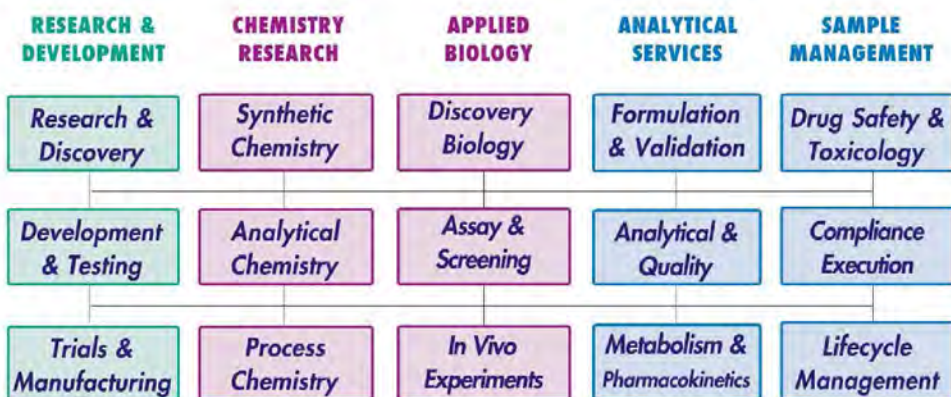
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